EXPIRED CARBON MONOXIDE AS A MARKER OF CO POISONING AND ITS APPLICATION IN DETERMINING TREATMENT END-POINTS

By

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DECLARATION OF ORIGINALITY

This thesis contains no material that has been accepted for the award of any other degree or diploma in any tertiary institution and to the best of my knowledge and belief, the thesis contains no material previously published or written by another person, except where this is referenced in the text.

I am responsible for the initiation and presentation of this thesis. The full extent to which others have contributed to the data contained herein is detailed in the acknowledgments.

David R. Smart

Date 27th August 2005

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Clinical data for controls and poisoned patients were collected at the Departments of Emergency Medicine and Hyperbaric Medicine at Fremantle Hospital, Western Australia, in 1992 and 1993 when I was working at Fremantle Hospital in Perth, Western Australia. The thesis has been prepared over 1994 to 2004 after I returned to Royal Hobart Hospital in February 1994.

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SUMMARY OF ABBREVIATIONS USED IN THIS THESIS

Abbreviation	Definition
ATA	Atmospheres absolute = the pressure relative to a vacuum (1 ATA = 101.3 kilopascals)
CI	Confidence interval (statistical)
CNS	Central nervous system
CO offgassing	Process of carbon monoxide being excreted in the breath as it is eliminated from the body
CO	Carbon monoxide
COHb	Carboxyhaemoglobin
COHb%	Carboxyhaemoglobin percent = the amount of carbon monoxide bound to haemoglobin, expressed as a percentage of total haemoglobin
CONSB	Carbon monoxide neuropsychiatric screening battery. A series of psychometric tests to measure cognitive function.
DCI	Decompression illness = a syndrome caused by the formation of nitrogen bubbles in the body of a diver after decompression from exposure to compressed air
DNS	Delayed neurological syndrome = a syndrome of delayed deterioration in neurological or cognitive function occurring 3-40 days after apparent recovery with acute treatment
ECG	Electrocardiogram = measurement of the electrical activity of the heart using skin electrodes
ED	Emergency department
ECO	Mean expired carbon monoxide concentration, expressed in parts per million

F_IO_2	Fraction of concentration of inspired oxygen, expressed as decimal 0 - 1.0, indicating of the relative amount of oxygen in the total inspired gas
FSQ	Functional status questionnaire
GCS	Glasgow coma score (scale 3-15) = description of conscious state Detailed in appendix 18.2.1
GHQ-12	General health questionnaire (12 questions)
Hb	Haemoglobin
HBO	Hyperbaric oxygen
HBOT	Hyperbaric oxygen treatment or hyperbaric oxygen therapy
HMF	Higher mental function
LOC	Loss of consciousness
LPG	Liquid propane gas
Min	Minute
MMSE	Mini-Mental State Examination. A cognitive function test with a score from 0 to 30. Detailed in appendix 18.2.2.
NBO	Normobaric oxygen = 100% oxygen breathed at ambient atmospheric pressure (Usually 101.3 kPa)
NNT	Number needed to treat. The number needed to treat using a therapeutic modality to gain one extra good outcome
O_2	Oxygen
P	Pressure
P_AO_2	Alveolar oxygen partial pressure
P_aO_2	Arterial oxygen pressure

P_IO_2	Pressure of inspired oxygen = the partial pressure of the inspired oxygen
PNS	Persistent neurological sequelae = persistent neurological or cognitive deficits after treatment for acute CO poisoning
ppm	Parts per million
PSIg	Pounds per square inch gauge pressure = the measured pressure in PSI, which is above ambient pressure
RMV	Respiratory minute volume = the amount of breath exhaled in one minute (litres)
SD	Standard deviation (statistical)

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2. THESIS ABSTRACT

Carbon monoxide (CO) is a colourless, odourless toxic gas that is able to substitute for oxygen at many levels in the oxygen cascade. CO poisoning is responsible for nearly a quarter of suicide deaths in Australia, and hundreds of individuals sustain non-fatal poisoning every year. Up to two thirds of individuals who survive CO poisoning have long-term neurological or cognitive impairment. Despite years of study by medical researchers, a reliable marker of acute CO poisoning severity that correlates with outcome has not been identified. Oxygen is known to be an antidote to CO poisoning, yet there is significant debate regarding the dose required, and the treatment duration. The end-point of CO excretion from the body is the lungs. Measurement of expired CO has been documented since the 1980's, however there has been limited study of ECO in poisoned patients.

In this research ECO was investigated as marker of CO poisoning, and its application in determining treatment end-point. A low cost, portable and non-invasive apparatus was successfully developed for measurement of ECO, oxygen concentration and minute volume. The apparatus was then evaluated in a variety of settings, for adults and children, and to establish baseline ranges for non-smokers, smokers and poisoned individuals, breathing air, NBO and HBO. The technique of measuring ECO was further investigated to determine the relationship between ECO and COHb, and for the diagnosis of CO poisoning. The apparatus was evaluated in the clinical setting to determine pulmonary CO elimination kinetics. A prospective series of CO poisoned patients was enrolled to determine if acute ECO levels correlated with clinical outcomes and to assess whether unrecordable ECO was a suitable marker of treatment end-point. In this research, expired oxygen concentration was also monitored, to ensure that all individuals received the stated dose of oxygen.

Baseline levels of ECO were found to be very low in healthy non-smoking volunteers, and in non-smoking divers treated for decompression illness, consistent with the observation that most CO derives from exogenous sources. Smokers had higher baseline ECO than non-smokers, and smoker ECO levels correlated positively with the number of cigarettes smoked per day, and negatively with the time since last cigarette.

Breathing air and NBO, a strong positive linear relationship between the ECO and COHb was observed for non-poisoned smokers, poisoned individuals and pooled data. Expired CO concentration increased in proportion with increasing F_IO_2 for 0.21 (air) to 1.0 (NBO). While breathing 100% oxygen,

increasing ambient pressure from 1 ATA to 2.8ATA did not alter the ECO concentration (ppm) in each breath. However, elimination of CO was greatly enhanced due to the increased density of gas at higher pressures. Each tidal volume at 2.8ATA actually contains 2.8 times as many molecules of CO compared with the same tidal volume at 1ATA ambient pressure. When poisoned subjects breathed NBO and HBO, significant amounts of ECO were detectable when the COHb was unrecordable using the biochemical method. This suggested that ECO more accurately reflected remaining CO in body stores than COHb, however this might have resulted from the limits of the biochemical method for detecting low levels of COHb (< 2%). Concurrent measurement of expired oxygen provided useful confirmation that the intended 100% oxygen dose was delivered to all treated individuals.

ECO was a useful non-invasive test to diagnose acute (< 6 hours) CO poisoning, when ECO values were > 40 ppm. For ECO values of 7 ppm to 40 ppm, clinical information would be needed to separate mildly poisoned individuals from smokers. Expired CO and COHb were equally effective in identifying acutely poisoned individuals, from smokers and non-smokers. Critical values of ECO >40 ppm or COHb > 7% were shown to be highly specific for CO poisoning.

Expired CO demonstrated single stage exponential elimination kinetics in both NBO and HBO treatment environments. CO elimination in HBO was significantly faster than NBO. There was a seven to ten-fold variation in CO elimination between individuals in either treatment (NBO or HBO). Based on these findings, current empirical regimens may over-treat some individuals and under-treat others. The half-lives determined for ECO elimination were longer than those determined for COHb. This suggests that elimination of CO via the breath may be slower than elimination from Hb. If unrecordable ECO proved useful as a treatment endpoint, this would allow treatment to be tailored to the individual's acute CO load.

In the clinical series of 66 acutely poisoned patients, there were a high number of males sustaining CO poisoning from deliberate self-harm. These individuals had longer exposures, greater neurological toxicity, and were more likely to have LOC than accidental exposures. The greater toxic effect and higher CO body load was most likely due to breathing leaded petrol exhaust containing high CO levels to attempt suicide. In keeping with their greater neurological toxicity, there was a positive correlation between ECO, COHb levels, and the severity of poisoning. The ECO measurement breathing oxygen correlated significantly with the severity of neurological impairment in the ED. This provided support for ECO levels as useful guide to acute clinical poisoning severity. However, acute ECO and COHb

levels measured in the ED were not predictive of outcome at 3 months. This may have been affected by significant delays in transferring patients for HBO treatment.

Just over 28% of patients had poor outcomes at 3 months, using unrecordable ECO as a treatment end-point. At this point, patients who had abnormal neurological or cognitive function remained abnormal at 3 months. Unfortunately the treatment endpoint using ECO did not prevent cases of DNS, or the need to provide follow-up for CO poisoned patients. The occurrence of DNS after all CO had been removed suggests that DNS may result from mechanisms other than direct CO toxicity.

Poor outcomes were associated with delays to study entry, suicide attempts, motor vehicle exhaust as a source of CO and acidosis measured in the ED. Individuals with LOC did not have a significantly worse outcome than those remaining conscious during their CO exposure. HBO and NBO treated patients had similar levels of PNS, however the HBO group had a lower incidence of DNS – an unexpected finding. Because the study was not randomized, it was not possible to conclude this is a definite treatment effect. Compared with NBO, HBO treatment led to faster removal of CO, and shorter treatments.

Measurement of ECO constitutes a novel non-invasive method of monitoring of acute CO poisoning. It has potential to compliment existing methods of monitoring acute CO poisoning, and may be useful as a non-invasive test to diagnose CO poisoning. Clinical outcomes in this series compared favourably with other series of similar severity poisoning in the literature. However, further research using a randomized controlled trial is required to determine if unrecordable ECO is a useful guide to treatment endpoint.

3. THESIS STRUCTURE

3.1. Introduction

Despite many years of study by medical researchers, a reliable marker of acute CO poisoning that correlates with outcome has not been identified. Oxygen is known to be an antidote to CO poisoning, yet there is significant debate regarding the dose required, and the treatment duration. To date there has been no method of tailoring treatment to the needs of the patient. In this research I planned to investigate ECO as diagnostic marker of CO poisoning, and its application in determining treatment end-point. As a novel marker of CO poisoning, the investigation of ECO presented some challenges: A portable apparatus capable of measuring ECO in a variety of clinical settings had to be developed from scratch. "Normal" ECO levels in healthy individuals were unknown. Little was known about the relationship between ECO and COHb or the effect on ECO when breathing 100% oxygen, or HBO. The elimination kinetics of CO via the lung in humans had not been studied. Expired CO had potential to be a useful marker of treatment endpoint, because CO had been detected in the breath of poisoned patients even after COHb returned to "normal". This suggested ECO was a late indicator of CO elimination from the body. There had been no investigation of ECO and the defacto "gold standard" indicators of outcomes of CO poisoning - neurological and cognitive assessment. Hence, to fully investigate the potential for ECO as a marker of treatment end-point in CO poisoning, a system of neurological and cognitive testing was also required to assess treatment outcomes.

3.2. Structure of the thesis

This research divided into the following chapters:

Chapter 4 describes the research aims**.**

Chapter 5 summarises current literature relevant to the thesis.

Chapter 6 summarises the development of an apparatus capable of measuring ECO in a variety of clinical settings. The apparatus needed to be portable and capable of sampling from adults and children, ventilated and spontaneously breathing individuals, and from patients being treated in the hyperbaric environment.

Chapter 7 describes the initial clinical evaluation of the apparatus and collection of control ECO samples from healthy individuals, including non-smokers and smokers. Measurements were performed

on divers treated at the Fremantle Hospital Hyperbaric Medicine Unit, to evaluate the effect of pressure on ECO from healthy individuals.

Chapter 8 outlines a prospective case series of CO poisoned patients, for the purpose of studying ECO as a marker of CO poisoning. In this chapter, the demographic features of these patients including their age, sex, smoking status, whether the poisoning was accidental or deliberate, the source of the CO, whether or not individuals had LOC, and their neurological status at presentation are examined. It also provides an overview how the case series was studied in chapters 9 – 15.

Chapter 9 examines the relationship between COHb and ECO breathing air, for control subjects and acutely poisoned individuals.

Chapter 10 investigates the relationships between ECO and COHb breathing air, NBO and HBO for acutely poisoned patients.

Chapter 11 describes use of the CO offgassing apparatus in the ED, for the diagnosis of CO poisoning. Breath samples from acutely poisoned patients were compared with smoker and non-smoker controls to determine if CO poisoning could be differentiated using ECO measurements.

Chapter 12 investigated the factors that affect CO load and the clinical consequences of CO poisoning. Factors examined included the length of exposure to CO, the intent of exposure (suicidal versus accidental), the source of CO, delays to oxygen treatment and study entry, and the neurological status of the patient in the ED.

Chapter 13 examines the detailed elimination kinetics for expired carbon monoxide from the lung. In this chapter, ECO was measured from poisoned patients treated with NBO and HBO.

Chapter 14 investigates the use of unrecordable ECO as treatment end-point in the case series of CO poisoned patients. The chapter examines the association between neurological outcomes at this point, with neurological and cognitive outcomes at 3 months.

Chapter 15 further investigates the factors that were associated with good and poor outcomes at 3 months in the case series of CO poisoned patients. Factors such as age, sex, smoking status, concomitant use of drugs or alcohol, aetiology of CO exposure, delays neurological rank in the ED, ECO and COHb levels, acidosis, and treatment method were correlated with outcome at 3 months.

4. THESIS AIMS

4.1. Research hypotheses

It is hypothesised that the mean concentration of expired carbon monoxide (ECO):

- is a suitable marker of carbon monoxide (CO) poisoning
- can be used for the diagnosis of acute CO poisoning and monitoring of response to treatment
- may be an effective indicator of body stores of CO
- is a marker of treatment endpoint in the poisoned patient

4.2. Research aims

The aims of this research were to develop and evaluate an apparatus capable of measuring ECO, determine ECO with COHb, investigate the phenomenon of CO elimination in human subjects, and then investigate ECO in the diagnosis and treatment of CO poisoning. The project was conducted in two stages:

(1) Development and evaluation of the CO off-gassing apparatus.

(a) Design and construct an apparatus to measure CO in the exhaled breath that was suitable for clinical sampling of ECO from subjects breathing air, 100% oxygen and hyperbaric oxygen (chapter 6).

(b) Evaluate the apparatus for clinical sampling from healthy non-smokers, smokers breathing air and oxygen, healthy divers breathing air, NBO and HBO, to determine mean ECO levels in these groups, and to investigate the relationship between smoking habit and ECO levels (chapter 7).

(2) A prospective case series of CO poisoned patients was enrolled to:

(a) Document their clinical and demographic characteristics including their age, sex, smoking status, whether the poisoning was accidental or deliberate, the source of the CO, whether or not individuals had LOC, and their neurological status at presentation (chapter 8). An additional aim of chapter 8 was to summarise how the case series was studied in chapters 9 – 15.

(b) To examine the relationships between mean ECO breathing air for non-smokers and smokers, and acutely poisoned patients, and COHb (chapter 9).

(c) Correlate ECO in three environments of P_IO_2, air, NBO and HBO, with COHb (chapter 10).

(d) Evaluate ECO measurement to diagnose acute CO poisoning in the ED and to correlate ECO with MMSE scores, to determine if ECO was useful in identifying impaired cognitive function consistent with moderate to severe poisoning (Chapter 11).

(e) Determine the factors that influence CO load and ECO in poisoned patients including the duration of exposure, the intent of exposure, the source of CO, the delay to initial oxygen treatment, delay to study entry, and the neurological status on arrival in the ED (chapter 12).

(f) Determine the elimination kinetics of CO using ECO measurements, compare these with elimination of CO from Hb and identify factors that may influence elimination kinetics in poisoned subjects such as age, sex and smoking status, and treatment with NBO or HBO (Chapter 13).

(g) Determine if unrecordable ECO was a useful treatment endpoint, by:

(i) correlating treatment to unrecordable ECO with acute recovery, and

(ii) correlating neurological status at treatment end-point, with the clinical outcomes PNS and DNS assessed at three-month follow-up using neurological and cognitive testing

(iii) To compare the case series outcomes with the results of other studies (chapter 14).

(h) Determine whether demographic factors, aetiology and severity of CO poisoning, delays to treatment and method of treatment, and patients self-reporting of symptoms had any relationship to outcomes at 3 months (chapter 15).

5. LITERATURE REVIEW

5.1. Carbon monoxide poisoning as a health problem

Carbon monoxide poisoning is a significant health problem. In 1996, CO poisoning accounted for nearly 22% of all suicides in Australia (Routley 1998). Non-fatal CO poisoning has an incidence of 18.1 cases per 100,000 population per year in USA (Hampson 1997). Non-fatal CO poisoning also results in significant morbidity. Acute CO toxicity predominantly affects the central nervous system and cardiovascular system (Myers and Thom 1995). In addition, some 10-40 percent of victims suffer delayed neurocognitive deterioration, which may result in permanent sequelae if not recognised and treated (Smith 1973, Jefferson 1976, Ginsberg 1979, Choi 1983, Myers et al 1985). High-risk groups for severe morbidity from CO include older individuals, particularly over 65 years of age, and individuals with pre-existing cardiovascular, cerebrovascular or pulmonary disease (Choi 1983, Thom 1989).

Suicide attempts resulting in CO poisoning

Carbon monoxide is produced from incomplete combustion of organic molecules and individuals choosing CO as a method of suicide tend to choose readily available sources. Studies of survivors of CO poisoning demonstrate that 19.9% to 69% are due to deliberate exposure (Gorman et al 1992, Weaver et al 2002, Scheinkestel et al 1999). In the 1960's, coal gas suicides accounted for over 50% of all deaths due to suicide (Routley 1998). When natural gas was substituted for coal gas in the UK, the rate of suicides due to this method decreased to almost zero (Smith and Brandon 1973). Australian Bureau of Statistics (1994) figures show that motor vehicle exhaust is the most common source of CO for suicide attempts, and the incidence is increasing. Deliberate exposure from motor vehicle emission occurs by direct connection of a hose to the vehicle exhaust, or parking the vehicle in a confined space with the engine running and the windows open (Stewart et al 1975, Mark 1992). Carbon monoxide production is maximal with a cold engine start than after the engine is warm, even with a catalytic converter. After a cold start, cabin CO levels reached 6000ppm in cars with catalytic converters that were experimentally set up to mimic suicide circumstances (Morgen et al 1998). This is sufficient to produce lethal levels of COHb. Human experiments have shown that exposure to 100 ppm CO for 4 hours in sedentary individuals can produce COHb levels of in excess of 12% (Peterson and Stewart 1970). Individuals attempting suicide by CO poisoning from car exhaust may ingest other toxic

substances such as alcohol, licit (predominantly sedatives) and illicit drugs (Hayward et al 1992). These substances lessen their chances of escape by compounding acute CNS depression and cognitive impairment at the time of their suicide attempt (Weaver et al 1996, Routley 1998).

Accidental CO poisoning and endogenous CO production

Accidental CO poisoning has been recorded from numerous sources. These include: house and building fires (Myers 1995), blast furnaces and coke ovens (Lewis et al 1992, Myers and Thom 1995), motor vehicle exhaust (Meredith 1988), powerboat exhaust (Hadley 1952, Silvers and Hampson 1995), operation of fork lift trucks indoors (Fawcett 1992), car park exhaust (Wright et al 1975, Fraser 1990), indoor use of welding equipment (Gibson et al 1991), poorly vented gas heaters and cooking apparatus (Kelly 1978, Du Peloux Menage and Everest 1990, Anonymous MMWR 1993), surface supply breathing apparatus (hookah equipment) for divers (Edmonds et al 1992), indoor use of kettle-style barbecues (Jelinek 1994), ice rinks from petrol driven ice smoothers (Paulozzi 1991), petrol generators during power blackouts (Cohen et al 1997) and methylene chloride paint stripper (Stewart and Hake 1976, Rudge 1990). Outdoor CO levels frequently exceed recommended 8-hour exposure limits in urban high traffic density intersections, and these may impact upon workers in these areas (Hewat et al 1998). Carbon monoxide may also be produced by degradation of inhaled anaesthetics by soda lime and baralyme absorbents (Fang et al 1995).

The catabolism of haem produces small amounts of endogenous CO that saturates 0.4% to 0.7% of the circulating haemoglobin (Stewart 1975). Environmental exposure to CO may elevate COHb to 1 - 2% in city-dwelling non-smokers (Ilano and Raffin 1990). A common source of CO is tobacco smoke. Tobacco smokers further saturate their blood to levels of 5 - 6 percent COHb, and some individuals may have levels of CO in the blood that are as high as 9% (Stewart et al 1974, Ilano and Raffin 1990).

CO uptake in the lung and binding with haemoglobin

CO uptake into the body, and combination with Hb is well described by a pharmacokinetic model known as the Coburn Forster Kane equation (CFKE). The model has been extensively tested in humans for COHb up to 20%, long low level and short high level exposures, as well as in laboratory animals. (Coburn et al 1965, Abboud et al 1974, Peterson and Stewart 1970 and 1975, Bernard and Duker 1981, Hauck and Neuberger 1984, Tikuisis et al 1992, Benignus et al 1993, Benignus et al 1994).

Figure 1 Coburn Forster Kane equation (CFKE) for steady state, (Coburn et al 1965).

$$[COHb] = [COHb_{end}] + [COHb_{ex}]$$

$$[COHb] = \frac{\dot{V}_{CO} . M . [O_2Hb]}{\bar{P}_cO_2} \times \left(\frac{1}{D_LCO} + \frac{P_B - P_{H2O}}{\dot{V}_A} \right) + \frac{P_ICO . M . [O_2Hb]}{\bar{P}_cO_2}$$

Where:

- [COHb] is the total COHb in the blood
- $[COHb_{end}]$ is the fraction from endogenous production
- $[COHb_{ex}]$ is the fraction from exogenous sources
- V_{CO} is the rate of endogenous production of CO in the body = 0.000333 x W in mL/min
- M is the Haldane affinity ratio (200 – 250)
- P_CO_2 is the average PO_2 in the pulmonary capillary = 101.6mmHg resting
- P_B is the pressure barometric (Usually 760mmHg)
- P_{H2O} is the vapour pressure (usually 47mmHg)
- P_ICO is the partial pressure of inspired carbon monoxide
- VA is the alveolar ventilation in ml/minute = 250 x $W^{0.74}$ mL/min
- O_2Hb is oxyhaemoglobin concentration
- D_LCO is the pulmonary diffusing capacity of the lung in ml CO per minute per mmHg = 0.027 + 0.563 x W (mL/min/mm Hg)

Values provided above are quoted in Benignus et al 1994, for healthy individuals based on their weight, (W = Weight in kg).

From the original work by Coburn et al (1965), $[COHb_{end}]$ in healthy individuals is very low; ranging between 0.21 to 0.43% at steady state. The main influence on total [COHb] is from exogenous inhaled CO. Detailed examination of the above equation reveals that [COHb] rises in proportional to the P_ICO and falls in proportion to the PcO_2. Carbon monoxide will displace oxygen to achieve a steady state concentration in proportion to the P_ICO. Inhaled CO crosses the alveolar membrane readily, a property that is used to measure the diffusing capacity of the lung in pulmonary function tests (American

Thoracic Society 1995, West 2000). Carbon monoxide has an affinity for haemoglobin (the M value or Haldane constant), that is 200 - 250 times higher than oxygen (Sendroy et al 1929, Allen and Root 1957, Rodkey et al 1969 and 1974). The relationship is expressed by the Haldane equation:

$$COHb / O_2Hb = M.(P_{CO} / P_{O2})$$

The high affinity of CO for Hb prevents any significant partial pressure developing in pulmonary venous plasma such that $P_aCO < P_ACO$ (Bruce et al 2003). However CO is much slower than oxygen to react with the haemoglobin moiety. When blood is shaken in 100% CO, it takes 20 minutes to reach 91% COHb saturation (Goldbaum et al 1976). Benignus et al (1994) demonstrated there was a lead time of up to 10 minutes to reach steady state COHb levels in humans exposed to high FICO (6700ppm), requiring time for arterial and venous admixture. In contrast, plasma oxygen partial pressure reaches almost 100% of alveolar level with Hb 97% saturated in only 0.3 seconds (West 2000). Despite the slower reaction of CO, its high affinity for Hb leads to a progressive rise in COHb to the steady state value predicted by the Coburn Forster Kane equation. In vitro experiments by Ainsworth et al (1967) demonstrated that Hb very tightly binds CO. When 10 ml of blood was mixed with CO, dissolved CO constituted only 0.001ml (0.05%) of a total of 2 ml bound to Hb. Given the relatively slow binding of CO to Hb, it is likely that CO is loaded into tissues concurrently as it forms COHb, from dissolved CO in the plasma, which in turn has been "topped up" by CO the lungs.

Loading of COHb results in a progressive fall in oxygen carrying capacity for the exposed individual. Carbon monoxide also shifts the HbO_2 dissociation curve to the left, reducing the unloading of oxygen, and contributing to tissue hypoxia (Douglas et al 1912, Weaver 1999, West 2000). Traditionally, the affinity of CO for Hb has been regarded as the sole reason for toxicity in CO poisoning, causing reduced oxygen carrying capacity of the blood and cellular hypoxia. Tables were published correlating the symptoms and signs of poisoned patients with the COHb level (Sayers and Davenport 1930). This is the "anaemic hypoxia" model (Fein et al 1980). Despite substantial evidence to challenge this model as the sole mechanism by which CO exerts its toxic effects, adaptations of this table have been reproduced in journals and text books as recently as 1998 (Routley 1998).

Measurement of COHb has not correlated well with clinical outcomes and has not proved reliable as a marker of outcome in CO poisoning. Norkool and Kirkpatrick (1985) noted no difference in ED COHb levels when comparing unconscious survivors with fatal CO poisoning victims. Myers and

Thom reported had similar findings in a series of 191 patients (Myers and Thom 1995). Mathieu et al (1985) were unable to predict outcome from CO poisoning or the occurrence of DNS by COHb levels, or the clinical status of the patient at presentation. Gorman et al (1992) also found no difference between the initial COHb levels of patients who had sequelae at one month versus those who had fully recovered. This lack of correlation with COHb may be due to the downstream toxicity of CO on the CNS, and possibly the absorption of CO into other body compartments.

Goldbaum's group undertook experiments using dogs to demonstrate that COHb was not by itself toxic (Goldbaum et al 1975, Goldbaum et al 1976). They studied several groups of dogs. The first group breathed 13% CO (balance air) for 15 minutes to produce COHb levels of 54 - 73%. All of these dogs died within 15 to 65 minutes. The second group of dogs received intraperitoneal injections of 100% CO, which produced COHb levels of 45 - 80% (mean = 60%). However, they showed no evidence of toxicity. The third group of dogs was exsanguinated and their blood replaced with a Ringer's lactate/dextran 70 solution to create anaemic controls with an average Hb of 42g/L (37% of original Hb). All of these dogs survived. A final group of dogs were exsanguinated as above but then transfused with blood containing 80% COHb, to produce final COHb levels of 57-64 percent (mean 60%). All of these dogs survived. The authors concluded that CO toxicity at tissue level requires an inward flux of CO, and not just CO attached to Hb. In Goldbaum's dogs that received transfusions of COHb, dissolved CO originated entirely from the dissociation of COHb, and there was no inward flux as a result of inhaled CO. Dissolved CO available to move into tissues would have been in very low concentrations, and overall CO flux would have been in an outward direction via the lungs. Benignus et al (1994) showed that during CO loading by inhalation of 6700 ppm CO in humans, arterial COHb exceeded venous COHb by as much as 6-12%. In experiments using dogs breathing 1.5 – 7.5% CO, Abboud et al (1974) demonstrated transient COHb levels greater than 60% in the aorta. It is possible that the deaths of dogs inhaling CO in Goldbaum's series may have been due to transiently higher COHb levels in the arterial blood, than were reflected in the venous samples taken during the study (Goldbaum et al 1976), rather than just tissue toxicity.

Inhalation of a high concentration of CO increases partial pressure of dissolved CO in the plasma of the pulmonary capillary, and facilitates formation of COHb, where CO binds to Hb with an affinity 200 to 250 times that of oxygen (Haldane and Smith 1897, Douglas et al 1912, Rodkey 1974, Piantadosi 1987). The CO is then transported to tissues, attached to COHb and dissolved in the

plasma. At tissue level COHb contributes to dissolved CO as CO moves down a partial pressure and concentration gradient to combine with tissue myoglobin and cytochromes (Piantadosi 1987).

Pregnant mothers who are exposed to CO demonstrate (an unfortunate) model of CO loading and elimination across more than one compartment. Fetal Hb has greater affinity for CO than maternal Hb, however it is slower to load and unload. After 10 hours exposure to 50 ppm CO, fetal COHb is 10 - 15% higher COHb than maternal COHb (Longo and Chin 1977, Myers and Thom 1995). This places the unborn child at greater risk than its mother. Fetal P_aO_2 is lower than maternal blood, and hypoxia is further exacerbated by the CO-induced leftward shift of the haemoglobin-oxygen dissociation curve. Once loaded with CO, the fetal Hb is also much slower to unload. Cramer reported a fetal death due to accidental maternal CO poisoning. The mother's COHb was 23.7%. Her COHb fell to less that 3% after breathing oxygen by mask for 8 hours (Cramer 1982). Within 48 hours of discharge, the mother returned to hospital reporting loss of fetal movement, and intrauterine death was confirmed by ultrasound. The fetus had COHb levels of between 25% (right ventricle) and 35.1% (liver and spleen) at autopsy. Persistence of maternal dissolved CO may have been a factor in maintaining fetal CO pressure gradients.

Binding with myoglobin

Myoglobin has 36 - 40 times the affinity for CO than it does for oxygen (Myers and Thom 1995, Glabe et al 1998), and accounts for 10 - 15 % of the total body CO stores in CO poisoning (Coburn 1970). In dog and rat experiments, COMb was as high as 38 to 153% of COHb (Coburn and Mayers 1971, Sokal et al 1984). Once steady state COHb is reached, in experiments using CO rebreathing, there was a steady decline in COHb over 10 to 40 minutes due to exchange of CO with myoglobin (Bruce et al 2003). This suggests that entry into the tissues takes longer than the loading of COHb. Carbon monoxide binding to myoglobin in skeletal and cardiac muscle has been detected at COHb levels < 2% (Coburn et al 1973). Myoglobin facilitates the transfer of oxygen from Hb to the cytochromes. Carbon monoxide interferes with this process. Myocardial function becomes compromised early because of its high oxygen extraction ratio. The rate of energy produced in isolated cardiac myocytes by oxidative phosphorylation falls significantly when COMb reaches 40% (Whittenberg et al 1993). Animal studies have demonstrated ischaemic ECG changes in association with the falls in blood pressure induced by CO poisoning (Ginsberg et al 1974, Takano et al 1981). This correlates with the frequently encountered history of postural syncope in human victims of

moderate CO poisoning and the induction of angina in susceptible individuals (Tibbles and Perrotta 1994, Allred et al 1989). The uptake and elimination kinetics of CO with myoglobin has not been studied. The ratio of cardiac carboxymyoglobin to circulating COHb is approximately 3:1 (Coburn 1970). This indicates that COHb levels do not accurately reflect body stores of CO, and probably not a useful parameter against which to titrate treatment endpoint.

Extravascular binding of CO

Extravascular CO may account for 10 to 50% of total body burden of CO (Coburn et al 1965, Luomanmaki and Coburn 1969, Coburn et al 1971, and Coburn et al 1973). While much of this is attached to myoglobin, some appears to be attached to other respiratory enzymes. Carbon monoxide transfer into the cell appears to be considerably slower than its uptake by Hb. Loading of CO into the extravascular space may take up to 60 minutes, is assisted by hypoxia, and contributes to the delays in reaching a steady state for [COHb] (Sjöstrand 1949). In experiments involving rabbits with a pneumoperitoneum breathing 1000 ppm CO, the COHb reached equilibrium in 90 minutes, whereas the CO concentration in the pneumoperitoneum took 15 hours equilibrate and 10 hours to disappear (Gothert and Malorny 1969). Similar delays have been noted for CO to be transferred to the fetus in experiments using sheep, two hours for the maternal Hb to reach equilibrium versus 8-10 hours for the fetus. The elimination of the CO also matched this pattern (Longo and Hill 1977). In addition to myoglobin, CO also binds to cytochrome a3 oxidase, cytochrome c oxidase, reduced cytochromes of the p 450 types and tryptophan deoxygenase (Chance et al 1970, Piantadosi 1987, Coburn and Forman 1987, Brown and Piantadosi 1989). In vitro studies have shown that the cytochromes bind CO nine times less readily than they bind oxygen, and for CO to bind to cytochrome c oxidase, significant mitochondrial hypoxia must be present (Keilin et al 1939). Carbon monoxide binding with cytochromes is enhanced in hypoxia and in the presence of CO concentrations of 5000 -10000 ppm (Ball et al 1951, Piantadosi 1987). Coburn and Forman (1987) found that CO binding to cytochrome p450 requires COHb levels of 20%. Mitochondrial enzymes eventually become overwhelmed in a high CO partial pressure environment, exacerbated by hypoxia that results from increased [COHb] (Piantadosi 1996). There is evidence that the oxidation-reduction state of the cytochromes is dynamic and not uniform throughout the body. For example the cerebral cortex cytochrome oxidase has a high resting reduction level at normal oxygen tensions (Kreisman et al 1981, Piantadosi 1987). This results in CO binding to cerebral cytochrome oxidase more readily than other tissues in the body and may occur under physiological circumstances (Piantadosi 1985, Piantadosi 1987). This is also consistent

with the clinical effect of CO toxicity, which has a predilection for the central nervous system (CNS). Further evidence for multiple body compartments originates from Anderson's data. Anderson (1978) treated patients until COHb was undetectable, however several hours later, levels of COHb increased significantly due to release of CO from tissue sites.

Lipid peroxidation

Some authors have investigated the association between lipid peroxidation and CO poisoning because of similarities noted between CO poisoning and CNS reperfusion injury. Oxidation of unsaturated fatty acids (lipid peroxidation) has been demonstrated after brief ischaemic insults to the brain (Yoshida et al 1980, Kontos 1989, Linus et al 1990, Sakamoto et al 1991). Most of the injury is thought to occur when perfusion is restored. Reperfusion injury is postulated to occur from oxygen free radicals causing oxidative damage to tissues (Kontos 1989), particularly highly reactive "second generation" free radicals that produce lipid peroxidation (Myers and Thom 1995). This oxidative injury has been studied using markers such as xanthine oxidase. Xanthine oxidase is able to generate free radicals using oxygen as an electron acceptor. In animal studies, increased levels of xanthine oxidase have been demonstrated in the brain after CO poisoning, similar to that observed with reperfusion injury (Thom 1990, Thom 1992). Some of the effect of lipid peroxidation may be mediated via neutrophils adherent to the brain microvascular endothelium (Thom 1990).

CNS toxicity

The anaemic hypoxia model does not explain the CNS toxicity of CO. In the last two decades, clinical studies have focused on neurological and cognitive function to assess outcome, and evidence is accumulating to shed light on the cellular effects of CO in the brain. A number of other processes can generate free radicals in the brain. These include: disturbances to the mitochondrial electron transport chain, phospholipase activation and excess excitatory neurotransmitter release (Yoshida et al 1980, Kinuta et al 1989, Kontos 1989). The last factor is mechanism by which CO may mediate its toxicity in its role as a stimulator of cellular cyclic guanosine 3'5' monophosphate (GMP). Carbon monoxide may play a role as a neural messenger, regulating cyclic GMP in areas deplete of nitric oxide (Verma et al 1993). Haem-oxygenase-2 is located in the brain in high concentrations in the olfactory bulb, hippocampus, and islands of Callejae, piriform cortex, pontine nucleus, habenula, tenia tecta and cerebellum. There is no red cell catabolism at these sites. There is localisation in similar areas of the brain of cyclic GMP, cytochrome p 450 and haem-oxygenase-2. Cytochrome p 450 reductase serves as

an electron donor to haem-oxygenase-2. Exogenous CO may mediate some of its neural damage via this haem-oxygenase-2 system causing over stimulation of cyclic GMP and "excitatory neuronal degeneration" - a phenomenon observed in domoic acid toxicity (Teitelbaum et al 1990) and ischaemic damage potentiated by nitric oxide (Desphande 1993). Interstitial glutamate concentration increases in the hippocampus during and after CO poisoning (Piantadosi 1996). In another study Piantadosi et al (1997) found significant increases in glutamate and hydroxyl radical generation in rat brains after hypoxia. Learning and memory deficits were noted in the rats, which correlated with delayed structural damage in the frontal cortex, cerebellum and globus pallidus. It has been suggested that the clinical syndrome of delayed neurological sequelae may be explained by neuronal cell apoptosis (Piantadosi 1997). Permanent neurological injury may result from severe toxic effects of CO in susceptible areas of the brain - the hippocampus, globus pallidus, specific layers of the cerebral cortex and cerebellum, and the substantia nigra (Lapresle and Fardeau 1967, Sawada et al 1980, Ginsberg 1985, Horowitz et al 1987). There is evidence that the damage to the hippocampus from CO can be inhibited by the glutamate antagonist N-methyl-D-aspartic acid (Ishimaru et al 1992).

Imaging studies, clinico-pathological correlations

Most of the above studies have occurred in animals, and whether or not this data can be extrapolated to humans is unknown. There are however similarities in the CNS injury patterns found in humans, with the propensity for CO to produce focal damage in specific brain regions. Areas of the brain noted to be damaged at post mortem in CO poisoned humans have been the hippocampus, laminar necrosis of the cerebral cortex, cerebellum, basal ganglia including the globus pallidus and substantia nigra (Richardson et al 1959, Lapresle and Fardeau 1967, Sawa et al 1981, Kanaya and Kamada 1993, Pracyk et al 1995). Authors in the 1990's likened CO sequelae to anoxic encephalopathy (Tibbles and Perrotta 1994, Segar and Welch 1994). Both CO and other causes of anoxia may result in brain injury that never recovers after the initial insult (Plum et al 1962). However, if carbon monoxide were acting purely by producing "anaemic hypoxia" then it would be expected that a more diffuse injury pattern would occur, consistent with anoxic encephalopathy (Ginsberg et al 1976, Vierregge et al 1989). Hence, the "anoxic" theory is an oversimplification of the fundamental pathological effects of CO.

Neuro-imaging studies have confirmed focal lesions in severely CO poisoned victims in areas of the brain that are similar to those found at post mortem (Sawada et al 1980, Sawa et al 1981, Sawada et al 1983, Horowitz et al 1987, Lind et al 1991, De Reuck et al 1993, Hopkins et al 1993, Pracyk et al

1995). Van Meter's group in 1994 showed that HMPAO single positron emission computed tomography scanning was able to demonstrate perfusion and metabolic deficits in the CO-poisoned brain that correlated with the patient's clinical status. Animal studies have also confirmed focal injury patterns. Hippocampal damage from CO has been observed in rats (Hopkins et al 1992, Tomaszewski et al 1992), and this leads to defective maze navigation performance, which is prevented by HBO (Tomaszewski et al 1992, Bunegin et al 1997). Effects in glucose metabolism in the hippocampus and globus pallidus at 5 days post CO exposure have been correlated with learning dysfunction (Thom 1997). The hippocampus is more affected by CO than it is by hypoxia (Doolette 1991). Damage to the hippocampus from CO has been correlated with impaired cognitive function tests (Hopkins et al 1993). This demonstrates a link between the pathological and clinical effects of CO, particularly in relation to memory deficits.

Combined Effects

In animal studies the neurological damage is greatly enhanced by concomitant hypotension or occlusion of the carotid artery during exposure (Laas et al 1983, Okeda et al 1982). Severe brain injuries have occurred in areas with poorly developed anastomotic blood supplies, correlating with the degree of hypotension (Ginsberg et al 1974). This is consistent with the anaemic hypoxia/hypotension model that is strongly supported by some authors (Olson 1984). There are however, other mechanisms operating in CO poisoning which produce focal brain injury. Combinations of effects may contribute to the final clinical picture and pathophysiology from CO poisoning. It is likely that all of the above pathophysiological mechanisms contribute to the acute toxic effect of CO, which at some point, may result in irreversible neurological damage. Delayed neurological deteriorations are more likely to result from the downstream tissue and intracellular effects of CO. These appear to be reversible with HBO, however if not treated, may become irreversible (Myers et al 1985, Smith and Brandon 1973).

Weaver in 1999 summarised the mechanisms by which CO may be detrimental to humans:

1. Cellular hypoxia caused by COHb formation
2. The leftward shift of the oxyhaemoglobin dissociation curve
3. A direct cytotoxicity role in which CO can interfere with utilization of molecular O2 and production of ATP.
4. CO binding to myoglobin, interrupting muscle O2 transport
5. CO binding to P450, interfering with various enzyme functions

6. CO hypoxia contributes to significant oxidative stress manifested by increases in catecholamine levels and in elevated levels of reactive O2 species.

7. CO poisoning causes brain lipid peroxidation attributable to the inactivation of neutrophils (ischaemia-reperfusion injury)

8. CO by interacting with platelets, causes endothelial deposition of peroxynitrate and vascular damage

9. Apoptosis may also contribute to CO-related pathology

Available evidence suggests that CO has far more extensive adverse effects that just forming COHb.

Elimination kinetics of CO from blood and tissue stores

Carbon monoxide is eliminated almost exclusively via the lung except for a small amount that is oxidised to CO_2 in the tissues (Piantadosi 1987). Most studies using COHb as a marker of CO elimination have demonstrated single exponential function kinetics (Piantadosi 1987).

Most studies of CO elimination from the body have measured COHb as an indicator of body CO stores. Two previous studies have confirmed CO elimination from Hb is a single stage exponential process (Pace et al 1950, Peterson and Stewart 1970). Elimination is influenced by the pressure of inspired oxygen (Pace et al 1950, Peterson and Stewart 1970, Myers et al 1987, Piantadosi 1987, Levasseur et al 1996, Jay and McKindley 1997, Weaver et al 2000). The influence of P_IO_2 was confirmed in chapter 12 of my research. A study of dogs by Wagner et al found a biphasic decline in COHb, initially exponential, followed by a linear elimination (Wagner et al 1994). A summary of data from available studies is provided in table 5.1. Detailed examination of Peterson and Stewart's data reveals that there is considerable variability of elimination half-lives among individuals. In their series of 39 subjects, the half-lives in air ranged from 128-409 minutes. Other researchers have noted similar variation in the CO elimination half-lives for NBO (31.5 - 149.7 minutes) and HBO (4.2 to 86.4 minutes) (Myers 1987), and for NBO (26-148 minutes) Weaver et al (2000). Data from 45 patients studied by Levasseur and coworkers demonstrated a mean CO elimination half-life of 89 minutes (SD 38, range 34 to 180 minutes) breathing 100% oxygen (Levasseur et al 1996). In Levasseur's study, elimination was not significantly altered by the method of oxygen delivery, mechanical ventilation, or the source of the CO (fire victims versus gas water heaters).

Weaver et al (2000) found that the only factor influencing elimination half-life was the P_aO2. In Weaver's retrospective study, elimination half life was not influenced by gender, age, smoke inhalation, history of LOC, tobacco smoking status, degree of initial metabolic acidosis, or initial COHb level. Interestingly P_aO_2 was higher for patients ventilated via ETT (than for O_2 via face-mask), and COHb half life was lower in Weavers study. Weaver's discussion commented on the possibility of variableF_IO_2 being an influence on COHb removal via the face-mask. A significant part of the variability observed in CO elimination may be due to the presence of several tissue compartments (for example differing muscle mass), and physiological differences in tissue PO_2, differences in cardiac output, pulmonary diffusing capacity and alveolar ventilation. There has been very little study of these factors in CO-poisoned patients. In addition, no previous studies have investigated the elimination kinetics of CO using ECO measurements. One of the aims of this thesis was to measure elimination of CO in the breath during NBO and HBO treatment and calculate ECO elimination kinetics.

Table 5.1 Summary of literature:
Elimination CO half-life at various inspired partial pressures of oxygen (P_IO_2)

Study	COHb Half-life			Comment
	Air (minutes) PIO2 = 0.21 ATA	**100%O2 (minutes) PIO2 = 1 ATA**	**HBO PIO2 as stated**	
Pace et al 1950 (15 subjects)	Male = 249 Female = 179	Male = 47 Female = 36	HBO 2.5 ATA Male = 22 Female = 15	Difference between sexes noted
Peterson and Stewart 1970 (25 subjects)	320	80.3	HBO 3.0 ATA 23.3	Four subjects only at 1.0 and 3.0 ATA
Wagner et al 1975 (Dogs, n=19)	COHb (5-16%) = 190 (20-43%)=134			Dog Studies
Myers et al 1987 **19 NBO subjects** **12 HBO subjects**		Mean = 131 SD = 133 Range (27.1 – 462.1)	HBO 3 ATA Mean = 43 SD = 22 (Range = 4.2 – 86.4)	Human studies COHb ranged from 5.1 to 60.5%
Levasseur et al 1996 **45 subjects**		Fire = 91 ± 38 Heater=87± 40		No air or HBO data
Jay and McKindley 1997 (12 subjects)		71.3 ± 9.9	HBO 1.58 ATA 26.3 ± 3.7	No air data *Gamov bag for HBO Very low COHb
Weaver et al 2000 (93 subjects)		All = 74 ± 25 (Range 26 – 148) Male = 77 ± 25 Female=67 ± 23		No air or HBO data PaO_2 correlated with lower T ½ Lower T ½ and higher PaO_2 for ventilated via ETT than face mask

* Gamov bag = a pressurised plastic bag normally used for field treatment of high-altitude sickness

The end-point for elimination of CO from the body – expired CO

Studies by Bruce et al (2003) suggest that a multiple compartment model of CO uptake and elimination may be more appropriate than solely focusing on COHb. There is a slow transfer of CO between Mb and Hb, hence washout of the muscle tissue compartment may take much greater than twice the washout from the circulation (Petersen and Stewart 1970, Shimazu 2001). This may lead to

prolonged low level excretion of CO from myoglobin, via COHb and expired CO, long after COHb has apparently returned to "normal" levels. Study of multiple body compartments simultaneously requires a complex mathematical model (Bruce et al 2003). A potential method of simplifying this process is to concentrate only on the final end-point for CO elimination from all compartments; via the expired breath from the lung (Coburn 1965). End-tidal carbon monoxide excretion was shown by Vreman et al (1996) to correlate well with COHb in adults (COHb % = 0.25 x EtCO ppm), and a similar positive correlation was determined by Wickramatillake (1999) when validating the Dräger Ecolyser® apparatus. Vreman et al also demonstrated that EtCO increased in term newborns to levels > 3 ppm during haemolysis; due to endogenous CO production via activation of haem-oxygenase. Similar elevation of ECO has been observed for haemolysis associated with sickle cell disease (Sylvester et al 2003). Other authors have shown elevations of ECO in asthma, upper respiratory tract infections and cystic fibrosis (Zayasu et al 1997, Horvath at al 1998, Yamaya et al 1998, Terheggen-Lagro et al 2003). In all cases due to respiratory disease, the levels of ECO were less than 7 ppm in non-smokers. Deveci et al 2005 suggested exhaled CO values of less than 6.5 ppm may distinguish non-smokers from smokers.

Despite the technique being available for many years, there has only been limited study of ECO in poisoned patients (Willms et al 1985, Langston et al 1992, Mathieu et al 1999). It was logical that ECO should be further investigated as a marker of CO poisoning. There was no commercially available apparatus for sampling ECO from poisoned individuals.

Hence the first aim of my research was to construct an apparatus that could analyse CO in the exhaled breath for use in clinical settings relevant to CO poisoning.

Coburn et al (1965) were the first to mathematically link exogenous CO with the [COHb] occurring in steady state. Their equation predicted that in steady state, the [$COHb_{ex}$] would rise by 0.39% for each 2.2 ppm inhaled CO (corresponding to 1% rise in [$COHb_{ex}$] for 5.6 ppm inhaled CO. Conversely, if the individual is in steady state, loaded with COHb from an exogenous source, and breathing air that had negligible CO in the rescue environment, then the ECO would be expected to reflect the [COHb] in a similar ratio.

Expired CO has been used as a marker of abstinence by quit-smoking groups (Jamrozik et al 1984). Cigarette smoke may contain up to 4% CO. Carbon monoxide absorbed by smokers is excreted in the breath during intervals between cigarettes. Relapses are easily detected by measuring elevated CO

levels in the breath. The Bedfont Smokerlyser® was successfully used by Jamrozik and colleagues to measure exhaled CO in their program (Jamrozik et al 1984. Measurements from quit-smoking programs also provided a starting point to gauge ECO levels expected in the poisoned patient. In quit-smoking programs, expired CO measurements ranged up to 50 parts per million, depending on the number of cigarettes smoked, and how recently the last cigarette was consumed. The value of 30 ppm measured by the Bedfont apparatus correlated with a carboxyhaemoglobin (COHb) level of 6% (Bedfont Scientific, undated). Assuming a linear relationship between COHb and ECO levels according to this data, the expected range for ECO in poisoned patients would be 0 - 300 ppm (allowing for a COHb of up to 60%). Deveci et al (2004) measured exhaled carbon monoxide in smokers (17.1 ± 8.5 ppm) and non-smokers (3.6 ± 2.1 ppm), which were similar to the values measured by other authors of 16.4 ppm for smokers, and 1.3 ppm for non-smokers (Cunnington and Hormbrey 2001).

Because of limited study of the ECO and COHb relationship, a second aim was to investigate the relationship between ECO and COHb in healthy non-smokers and smokers, while breathing air.

The relationship between ECO and COHb has not been fully investigated in the literature, in particular there is very little data on poisoned individuals. Willms et al (1985) demonstrated that CO is detectable in the breath of CO poisoned patients even after COHb returned to "normal", however they did not document specific COHb levels that defined "normal", or the relationship between COHb and ECO. Willms group's early work was not developed further. Bedfont stated that the relationship between ECO and COHb was linear with a gradient of 5.0 ppm/% COHb (Bedfont Scientific Limited, undated). My search identified only one report of a poisoned individual, correlating ECO with COHb (Wallace 1998). Wallace reported value of 180 ppm CO corresponded to a COHb = 26% (a ratio of 6.9 ppm/% COHb).

The effect of increased F_IO_2 on ECO has received very little study in humans. Skrupskii et al (1995) demonstrated in rats that CO elimination in the breath increased as the F_IO_2 increased. The usual treatment for CO poisoning is high flow or 100% oxygen at 1 ATA (NBO), or at 2.0 to 2.8 ATA (HBO) (Myers et al 1985, Raphael et al 1989, Gorman et al 1992, Thom et al 1995, Mathieu et al 1998, Scheinkestel et al 1999, Weaver 1999, Weaver et al 2002, Hampson and Little 2005). Mathieu et al (1999) reported in abstract only, the relationship between end-tidal CO and COHb. A significant linear relationship was found between end-tidal CO (EtCO) and COHb for 79 patients. They found

that COHb (%) = 0.12 x EtCO ppm. This corresponded to a gradient of 8.33 ppm EtCO/% COHb. The gradient increased to 11.1 when patients were treated in HBO, indicating that there was a modest increase in CO elimination in the breath when breathing oxygen. End-tidal CO values are higher than mean ECO, because they reflect peak expired concentrations rather than the average across inspiration and expiration. This average is reduced by the ratio of dead space to tidal volume, which in healthy adults is 0.2-0.35 during resting breathing (West 2000). Extrapolating this data to comparing mean ECO with EtCO suggests that ECO would be 20 to 35% lower than the EtCO. My literature search was unable to source any studies directly comparing ECO with EtCO.

A further aim was to correlate ECO with COHb in three P_IO_2 environments; air, NBO and HBO. The last two reflected current treatment P_IO_2 environments from poisoned patients.

Consistent with the limited amount of research into ECO, there is also limited data on its utility as a diagnostic tool for CO poisoning. Mathieu et al (1999) quoted a value of ECO=50 ppm to diagnose CO poisoning with an accuracy of 91%. They did not however report a control group, and there was insufficient detail in their abstract to support their quoted value. Based on this limited data, ECO may be useful to diagnose CO poisoning. The diagnosis of CO poisoning is often difficult because the clinical features of CO toxicity are non-specific (Barret et al 1985, Dolan 1987, Heckerling 1987). The clinical effect of acute carbon monoxide poisoning is depression of neurological function (Myers et al 1985, Norkool and Kirkpatrick 1985, Gorman et al 1992). This manifests as impairment of conscious state, or cognitive function. Expired CO had the potential to be an acute marker of CO poisoning, but any study needed to be correlated with measurements of cognitive function.

One of the aims of the research was to evaluate ECO measurement to diagnose acute CO poisoning in the ED and to correlate ECO with MMSE scores, to determine if ECO was useful in identifying impaired cognitive function consistent with moderate to severe poisoning.

5.2. CO poisoning clinical patterns

Acute CO poisoning has been classified into mild, moderate and severe (Mark 1992). It should be noted however that there is some contention regarding these definitions because the condition of the poisoned individual presenting to the ED does not correlate with their final outcome at follow-up.

5.2.1. Mild CO poisoning

Mild CO exposure produces constitutional symptoms and pre-syncope but no loss of consciousness or cognitive deficits on neurological screening. There are frequently non-specific symptoms that mimic many other illnesses such as influenza. Headache is a very common finding and this may be exacerbated by exertion (Ellenhorn and Barccloux 1988, Kirkpatrick 1987). Difficulty in concentrating and a generalised feeling of fatigue accompany nausea, vomiting and light-headedness as the exposure increases. Because of the nonspecific nature of the symptoms, the diagnosis is frequently overlooked (Barret et al 1985), and may be missed in the Emergency Department (ED) (Heckerling et al 1988).

5.2.2. Moderate CO poisoning

Impairment of cognitive and higher mental function is usually demonstrable with moderate exposure to carbon monoxide. A transient loss of consciousness may have occurred with or without "mild" symptoms (Kirkpatrick 1987). Patients may appear detached or "vague". The higher mental function impairment is detectable using psychometric tests and the mini mental state examination. Ataxia and impaired balance as well as generalised muscle weakness accompany the impaired cognition. Objective measurement of cognitive function using the minimental state examination (Folstein et al 1975) or the Carbon Monoxide Neuropsychiatric Screening Battery (CONSB) (Meissner and Myers 1991) are useful to document the level of neurological impairment from CO as well as the response to treatment. Myoglobin facilitates the transfer of oxygen from Hb to the cytochromes. Carbon monoxide interferes with this process. Myocardial function becomes compromised early because of its high oxygen extraction ratio. Animal studies have demonstrated ischaemic ECG changes in association with the falls in blood pressure induced by CO poisoning (Ginsberg et al 1974, Takano et al 1981). This correlates with the frequently encountered history of postural syncope in human victims of moderate CO poisoning and the induction of angina in susceptible individuals (Allred et al 1989, Tibbles and Perrotta 1994).

5.2.3. Severe CO Poisoning

With severe CO poisoning, there is significant impairment of consciousness at the time of the acute exposure. Seizures occur in 1 to 3% of cases (Scheinkestel et al 1999). Deaths occur during the acute toxicity phase from cardiac arrhythmias and respiratory arrest (Mark 1992). As irreversible damage

occurs in the central nervous system, death may occur due to damage to vital centres responsible for control of respiratory and cardiovascular function. Those who are rescued, or successfully resuscitated, present with major neurological dysfunction, severe impairment of conscious state, agitation, coma and convulsions, cardiac arrhythmias, pulmonary complications and severe acidosis (Undersea and Hyperbaric Medical Society 1992). Patients may be difficult to manage, abusive or combative (Mark 1992).

5.2.4. Other Clinical Features of Poisoning

Cardiovascular abnormalities occur less frequently than neurological impairment. Sinus tachycardia or asymptomatic ST segment abnormalities may precede more sinister ventricular arrhythmias. Postural hypotension has been noted, and may be a cause of syncope. Up to 20 percent of patients with severe poisoning develop circulatory failure (Goulon et al 1986). Deaths due to ventricular arrhythmias are more common in individuals with cardiomegaly, or coronary artery disease (Ellenhorn and Barccloux 1988, Thom 1989). Electrocardiographic signs of ischaemia may be observed until the patient is oxygenated (Goulon et al 1986). Asymptomatic coronary artery disease may become manifest due to an exposure to CO. Respiratory system injury due to concomitant inhalation of other toxic substances in smoke is likely if the victim has been trapped in a fire. Aspiration pneumonia is a risk in unconscious patients, and pulmonary oedema occurs in up to 16% of victims (Mark 1990, Goulon et al 1986). Despite its continued inclusion in textbooks, the finding of cherry red skin discolouration is very rare (Dolan 1985, Gorman et al 1992, Mark 1992). Cyanosis or pallor is more frequently encountered. The venous blood may appear red due to high concentrations of COHb (Kindwall and Goldman 1984) but this is usually not clinically detectable.

Carbon monoxide poisoned patients may present with signs that are common to many unconscious patients who have remained in one position for extended periods. Pressure sores, skin blisters, rhabdomyolysis, myoglobinuria, neuropraxia, respiratory distress syndrome and sepsis may further complicate the cellular toxic effects of CO (Ellenhorn and Barccloux 1988).

5.2.5. Clinical evolution of CO poisoning

The clinical evolution of CO poisoning is summarised in figure 5.2:

(1) **Acute primary toxicity** (mild/moderate/severe)- usually reversible with oxygen

(2) **Secondary neurological injury** (moderate or severe)- diffuse or focal; may or may not be reversible. When irreversible, this is called persistent neurological sequelae (PNS).

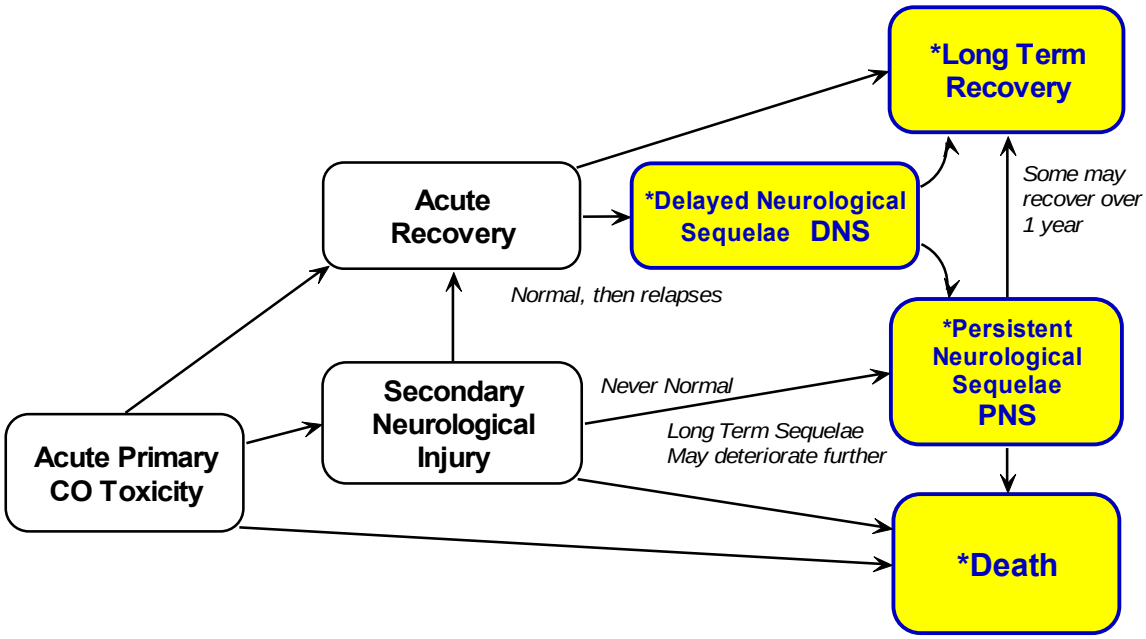
(3) Death may occur from (1) or (2) if not rescued

(4) **Recovery** (complete or incomplete) from (1) or (2)

(5) **Delayed relapse** = Delayed neurological sequelae (DNS) – this may recover, or lead to PNS

(6) **Recovery** (complete or incomplete) from (5)

Figure 5.2 - clinical progression of CO poisoning with outcomes *highlighted



Death related to CO poisoning may occur at any stage:

(1) During acute primary toxicity from acute hypoxia, cardiac arrhythmias, or hypotension.

(2) During secondary neurological injury due to deleterious effects on vital centres, or any of (1) above.

(3) Due to other causes (e.g. infections, pulmonary embolism, aspiration) secondary to long-term sequelae.

5.3. Outcomes of CO poisoning

Definitions

Sequelae from CO poisoning occur in two patterns: early morbidity and late (delayed) morbidity (Myers et al 1985, Gorman et al 1992). Patients with early morbidity may never recover from their CO poisoning and frequently have permanent neurological or cognitive abnormalities. Since Myers et al (1985) first identified the usefulness of psychometric testing in assessing CO poisoned patients, all investigators have undertaken some form of follow-up cognitive or neurological assessment to evaluate outcomes. Table 5.2 summarises the terms used to define neurological or cognitive impairment in assessing patient outcomes for the eight comparative and randomized trials of treatment for CO poisoning, published since 1985. Allowing for the different methods of measurement, there are considerable variations in the definitions used to define clinical outcomes for CO poisoned patients. For the purposes of this thesis it was necessary to develop some operational definitions:

Persistent neurological sequelae (PNS) may be defined as neurological or cognitive impairments (qv) that are present at discharge from hospital and remain with the individual at least to 1 month follow-up. Except for Ducasse et al (1985) and Thom et al (1995), all studies outlined in table 5.2 describe persistent neurological or cognitive abnormalities fitting this definition, although the time frames for follow-up vary considerably. There is also some evidence from randomized trials that PNS apparent at 6 weeks to 3 months may resolve by 12 months (Mathieu et al 1998, Weaver et al 2002). A more detailed discussion of PNS follows in section 5.3.2.

Delayed neurological sequelae are best defined as absence of cognitive or neurological abnormalities at discharge from hospital (using whatever method of assessment that is chosen), followed by neurological and/or cognitive function deterioration within the first six weeks after their poisoning. Patients with DNS may not recover, in which case it becomes PNS. Some patients with DNS have recovered with additional treatment using hyperbaric oxygen (Myers et al 1985). Because DNS occurs in the first 6 weeks after CO poisoning, any studies using follow-up at 6 weeks or beyond will be unlikely to detect it and all subjects with abnormal cognitive or neurological function are likely to be classified as PNS. This may have been the reason why Weaver's group initially powered their study to report DNS and PNS, and then changed to "cognitive sequelae" in their 2002 paper (Weaver et al 1995, 2002). It is possible that the two patterns of morbidity may occur by different mechanisms (toxic and/or hypoxic), that impact on the long-term outcome from CO exposure. To complicate matters further, patients with PNS can also deteriorate further with progression of their neurological or cognitive impairment (Smith and Brandon 1973, Choi 1983, Min 1986). This deterioration can only be

detected by longer term detailed follow-up. A more detailed discussion of DNS follows in section 5.3.3.

Table 5.2 Summary of definitions of cognitive or neurological abnormalities used by authors of comparative and randomised trials

Author (year)	Terminology to describe cognitive or neurological abnormality	Definition of Terminology	Timing of follow-up review	Comments
Myers (1985)	Recurrent Symptomatology Subacute Sequelae	Signs and symptoms of recurrent CO poisoning effects and confirmed abnormalities with psychometric testing	1 – 21 days then 6 – 12 months	
Raphael (1989)	Moderate Sequelae Severe Sequelae	One symptom of neurological dysfunction One abnormal neurological sign	1 month	
Gorman (1992)	Early Sequelae Late (Delayed) Sequelae	Abnormal neurological or psychometric test at hospital discharge Abnormal at one month not detected at discharge	Discharge 1 month	
Ducasse (1995)	Clinical abnormalities EEG abnormalities	Neurological signs and symptoms EEG	24 hours 3 weeks	
Thom (1995)	Delayed Neurological Sequelae	New symptoms and Deterioration of 1 or more Psychometric Test scores	Discharge 1 month	
Mathieu (1998)	Persisting neurological manifestations	Neurological examination at discharge Questionnaire regarding neurological symptoms and report from relatives/GP re behaviour	Discharge 1 month 3 months 6 months 12 months	
Scheinkestel (1999)	Persistent neurological sequelae Delayed neurological sequelae	Neuropsychological assessment abnormal at discharge and 1 month Neuropsychological assessment normal at discharge then abnormal at 1 month	Discharge 1 month	
Weaver (2002)	Cognitive sequelae	Neuropsychological assessment abnormal	Discharge 2 weeks 6 weeks 6 months 12 months	Initially powered to detect DNS, reported in abstract, but not reported in final paper

5.3.1. Psychometric (cognitive function) testing

Measurement of cognitive function is the only validated method of assessing outcome from non-fatal CO. Many studies have also shown that patient's scores on serial psychometric tests after treatment correlated better with outcome than the COHb level in the hospital ED (Mathieu et al 1985, Myers et al 1985, Norkool and Kirkpatrick 1985, Thom et al 1995, Scheinkestel et al 1999, Weaver et al 2002). Currently, the cellular effects of CO cannot be directly measured. Given that CO poisoning has a predilection for neurological injury, neurological and cognitive measurements are logical indicators of target organ injury. Psychometric testing varies in its complexity and methodology, but all tests provide assessments of cognitive function. The CONSB was a series of 6 tests that were validated by Messier et al in 1991 - (Myers et al 1983 (1 and 2), Myers et al 1985, Messier et al 1987 and 1991). Using psychometric tests and clinical findings, it is possible to identify PNS and DNS in affected individuals. Based on available literature, standardised psychometric testing should commence at the time of presentation and be monitored throughout the treatment. Follow-up should occur for a period of at least 3 months if the patient returns to normal, or up to one year if they are abnormal (Segar and Welch 1994, Olson and Segar 1995, Weaver 2002).

Many authors have attempted to use psychometric tests to guide acute treatment decisions. This strategy is unlikely to be successful because the degree of irreversible neurological injury can only be assessed retrospectively, after an extended period of follow-up (Segar and Welch 1994, Mathieu et al 1998, Weaver et al 2002). Complex psychometric tests have limited applicability during the acute phase of CO poisoning and do not appear to be a useful guide to acute treatment decisions. Complex psychometric tests are time-consuming to perform in a busy ED and results may be non-specific. Scheinkestel's group (1999) used a shorter test (MMSE – appendix 18.2.2) to assist with classifying their patients' severity of poisoning, and operationally this appeared satisfactory.

However, many victims are too severely poisoned to undertake testing, or may be initially affected by sedative substances. Lack of pre-exposure baseline data for each patient was raised as a problem in interpreting psychometric test results (Olson 1984). Some authors have criticised the psychometric tests due to the effect of observer bias, practice effect, and variability of results produced by the setting of the test. The authors asserted that recent events and illnesses in the individual being tested may affect results (Johnson et al 1991, Olson and Segar 1995, Segar and Welch 1994). Depression may be a confounding variable when assessing CO poisoned patients for delayed neurocognitive relapse.

There is a high rate of coexisting depression in individuals exposed to CO during acts of deliberate self-harm (Gorman et al 1992, Hay et al 2002), and possibly may adversely affect cognitive function. Jasper et al 2005 demonstrated that although individuals with suicide attempts and cognitive sequelae had a higher prevalence of depression and anxiety at 6 weeks, by twelve months this group were indistinguishable from those with accidental CO exposure. Jasper's group found that presence of depression did not appear to interfere with the cognitive testing used for CO poisoned patients. It is known that many individuals attempting suicide also have significant premorbid problems such as drug and alcohol abuse, which can affect test performance (Skopek and Perkins 1998, Hay et al 2002). Psychometric tests may overstate the degree of morbidity from CO poisoning in these individuals. Conversely, psychiatric disorders may be difficult to diagnose in the presence of the sequelae of CO poisoning (Jaeckle and Nasrallah 1985), or the PNS may be clinically similar to a psychosis. Despite these limitations, in the absence of other reliable markers of CO poisoning, serial psychometric tests have a significant role in measuring outcome of CO poisoning, after the acute toxicity phase. **Hence, in my proposed research to prospectively investigate ECO as a guide treatment end-point, the patient's post-treatment cognitive and neurological function will be tracked at discharge, during the first month, and then at 3 months to identify the clinically relevant outcomes of PNS and DNS.**

5.3.2. Persistent Neurological Sequelae

Persistent neurological sequelae occur when the neurological injury at the time of initial exposure is irreversible. In clinical series, these constitute the patients who *never* achieve normal neurological or cognitive status after poisoning. Persistent neurological sequelae may occur in frequencies ranging from 10 to 67 percent (Myers et al 1985, Yun et al 1987, Dinerman and Huber 1988, Gorman et al 1992, Mathieu et al 1998, Scheinkestel et al 1999, Weaver et al 2002). The clinical spectrum of persisting neurological and psychological disturbances resulting from CO poisoning has been documented for over 70 years (Grinker 1926, Shillito et al 1936). Sequelae include: cognitive deficits, personality deterioration and severe memory impairment, aphasia and impaired language function, agnosia, dementia, gait disturbance and apraxia, movement disorders such as Parkinsonism, choreoathetosis, incontinence, hearing loss, cortical blindness, and visual agnosia (Grinker 1926, Shillito et al 1936, Smith and Brandon 1973, Jefferson 1976, Sawa et al 1981, Werner et al 1985, Sparr et al 1991). However, even patients with severe neurological impairment from CO who appear

not to recover acutely may improve over time, with improvement documented to 12 months (Sawa et al 1981, Mathieu et al 1998, Weaver et al 2002). In a preliminary report of a prospective longitudinal study of CO poisoned patients, Weaver et al demonstrated that 40% had ongoing subjective symptoms, and 25% had objective abnormalities on neuropsychological screening 12 months after their CO poisoning (Weaver et al 2002). This compared with 50% (subjective) and 25% (objective) at six weeks post CO exposure. A prospective, randomized study of 575 CO poisoned patients by Mathieu et al (1998) demonstrated significantly less persistent neurological manifestations in the HBO treated group at 3 months compared with the group treated with NBO for 12 hours (9.5% versus 15%). By 12 months, this difference was not significant (Mathieu et al 1998). Mathieu's study demonstrated that the natural history of CO induced neurological injury is to improve over time, after NBO and HBO treatment. A faster recovery occurred after treatment with HBO. Some of the victims of CO poisoning have subtle neurological abnormalities that can be detected only using neuropsychological testing (Jefferson 1976). This stimulated the development of a Carbon Monoxide Neuropsychological Screening Battery (CONSB) (Meissner and Myers 1991), then progressively more sophisticated measures of outcome in 8 prospective comparative and randomized trials published since 1985 (Myers et al 1985, Raphael et al 1989, Gorman et al 1992, Ducasse et al 1995, Thom et al 1995, Mathieu et al 1998, Scheinkestel et al 1999, Weaver et al 2002). Segar and Welch (1994) recommended that standardised serial neuropsychological testing be used to assess all victims of CO poisoning. Despite these recommendations, there are considerable differences in the methods of outcome assessment in the above 8 comparative and randomized clinical trials.

Significant factors resulting in mortality and persistence of early morbidity from CO are the duration of exposure to CO (Mathieu et al 1985, Vezzani et al 1997), and the time from rescue to definitive treatment (Goulon et al 1986, Raphael et al 1989, Thom et al 1995). The development of permanent injury at the time of poisoning may be due to the combined effects of CO toxicity with hypoxia and reduced cardiac output. This has been observed in some animal studies, and was associated with a longer exposure (Laas et al 1983, Mathieu et al 1985, Okeda et al 1987, Vezzani et al 1997).

Some studies have attempted to correlate time to NBO or HBO treatment with clinical outcome. Less than six hours was associated with a more favourable outcome, particularly if HBO is used (Goulon et al 1986, Raphael et al 1989, Thom et al 1995). Goulon et al (1986) found that mortality was 13.5% if HBO was received < 6 hours after poisoning versus 30.1% if > 6 hours group. Mathieu et al (1998)

demonstrated a greater than 95 percent recovery at 12 months for 575 non-comatose patients treated with NBO or HBO within 12 hours of exposure. Very few studies report the time to using NBO (Raphael et al 1989, Thom et al 1995, Mathieu et al 1998). Table 5.3 describes recent prospective comparative and randomized controlled trial outcome data for PNS, as defined above .

Table 5.3 Persistent neurological sequelae prospective comparative and randomized controlled trial data

Table Key: P = Prospective, R = Randomized, S = Single blinded (outcome assessor blinded to treatment), D = double blinded (patient and outcome assessor blinded to treatment), U = Unblinded

Author and Year	Trial Design	Number in study	Entry Criteria	Treatment	Follow-up % and Period	Method of Outcome Measurement	% Deaths	Outcome Description	Comments
Raphael et al 1989	P, R, U	629 (343 in HBO vs NBO)	Admitted <12H No LOC	HBO 2ATA for 2H + 4H NBO vs 6H NBO	89% at 1 Month	Self reporting of symptoms Return to usual work. Unblinded Neuro exam	Nil in either group, 0.7% overall	NBO PNS = 50/148 (33.8%) HBO PNS = 51/159 (32.1%) p = 0.75 Not Significant	Data Represents 54.5% of total study
Gorman et al 1992	P, S	100	Consecutive series, all adults referred to hyperbaric centre.	NBO duration not stated HBO 1 x 2.8ATA for1H, or ≥ 2 x 2.8ATA for 1H	76% at 1 month	Blinded Neuropsychiatric tests	Not Stated	NBO PNS = 2/8 (25%) One HBO PNS = 9/20 (45%) Multiple HBO PNS = 9/50 (18%)	p = 0.039 favours multiple HBO vs other
Ducasse et al 1995	P, R, S	26	Moderate CO poisoning < 12 hours since exposure, GCS > 12, time to NBO < 2 H	HBO = 2.5ATA for 2H, 4H NBO, then 50% O_2 6H NBO = 6H NBO then 50% O_2 6H	69% at 3 weeks	Clinical at 12H, EEG at 3 months	Nil	NBO 5/12 abnormal clinically at 12H and 40% abnormal EEG at 3 weeks HBO all normal clinically at 12H, and nil abnormal EEG =at 3 weeks	No correlation with neurological or cognitive function
Mathieu et al 1998	P, R, S	575	CO Poisoned < 12H Non comatose COHb > 10% Not Pregnant	HBO 90 minutes 2.5 ATA NBO = 15LPM face mask for 12H	100% at 12 months	Blinded neurological assessment at discharge, then phone or GP questionnaire at 1,3,6,12 months	Nil	Difference noted at 3 months, no difference at 1,6, 12 months NBO PNS = 42/234 (15%) HBO PNS = 26/273 (9.5%) p = 0.016 at 3 Months favours HBO	All patients were discharged normal neurological examination
Scheinkestel et al 1999	P, R, D	191	Sequential admission, CO poisoning, no time limit Median HBO=7.3H NBO=6.1H	All had 3 days high flow O_2 by mask with reservoir. HBO 2.8ATA for 1H or NBO for 1H x 3 as daily doses	46% at 1 month	MMSE Blinded Neuropsychiatric tests	HBO 3/104 (2.9%) NBO 3/87 (3.4%) NS	(a) Severely Poisoned NBO PNS = 44/67 (65%) HBO PNS = 61/72 (85%) p = 0.03, favours NBO (b) Not Severely Poisoned NBO PNS = 15/20 (75%) HBO PNS = 16/32 (50%) p = 0.04, favours HBO * (*Analysis by Kehat and Schupak 2000)	MMSE used symptoms/unblinded assessment at 3 days to decide second course of 3 treatments
Weaver et al 2002 Some outcome data reported Weaver 2001*	P, R, D	152	Age>15 Not pregnant poisoned < 24H 2/3 enrolled < 6 Hours	HBO or NBO X3 over 24H	95% at 6 weeks 84% at 12 months	Blinded Neuropsychiatric Tests at 2 weeks, 6 weeks, 6 months and 12 months "Cognitive sequelae" used to define PNS	Nil in enrolled patients, 4 deaths-potential subjects	At 6 weeks HBO PNS = 25% , NBO PNS = 46% p = 0.007 favours HBO At 12 months HBO PNS = 18.4% , NBO PNS = 32.9% . p = 0.04 favours HBO	Prechamber cerebellar abnormality associated with PNS (OR=5.71) * HBO better if LOC, COHb>25%,Age>50, metabolic Acidosis

Table 5.4 Delayed neurological sequelae prospective comparative and randomized controlled trial data

Table Key: P = Prospective, R = Randomized, S = Single blinded (outcome assessor blinded to treatment), D = double blinded (patient and outcome assessor blinded to treatment), U = Unblinded

Author and Year	Trial Design	Number in study	Entry Criteria	Treatment	Follow-up % and Period	Method of Outcome Measurement	% Deaths	Outcome Description	Comments
Myers et al 1985	P, U	213	All Adults and children sequential admission, CO poisoned time not stated	HBO 2.8 ATA or NBO to COHb<5%, duration not stated	100%	Unblinded Neuropsychiatric tests CONSB	Nil in either treated group	NBO DNS = 10/82 (12.2%) HBO DNS = 1/131 (1.0%) p < 0.001 favours HBO	PNS not reported All relapses successfully treated with HBO
Gorman et al 1992	P, S	100	Consecutive series, all adults referred to hyperbaric centre.	NBO duration not stated HBO 1x 2.8ATA for 1H or ≥2 x 2.8ATA for 1H	76% at 1 month	Blinded Neuropsychiatric tests	Not Stated	NBO DNS = 2/8 (25%) One HBO DNS = 2/20 (10%) Multiple HBO PNS = 0/50 (0%) p = 0.014 favours multiple HBO vs other	
Thom et al 1995	P,R,U	65	Adults < 6H post CO exposure Mean time to O2=1.1H, Mean time to HBO = 2H	HBO 2.8 ATA 30 min, then 2.0 ATA 90 min NBO until all symptoms gone mean = 4.2H	100% at 3 months	Unblinded neuropsychiatric Tests	Nil	NBO DNS = 7/32 (22%) HBO DNS = 0/33 (0%) p = 0.014 favours HBO	Unblinded neuropsychiatric testing
Scheinkestel et al 1999	P, R, D	191	Sequential admission, CO poisoning, no time limit Median HBO=7.3H NBO=6.1H	All had 3 days high flow O2 by mask with reservoir. Then HBO 2.8ATA or NBO x 3	46% at 1 month	MMSE Blinded Neuropsychiatric tests	HBO 3/104 (2.9%) NBO 3/87 (3.4%) NS	NBO DNS = 0/87 HBO DNS = 5/104 p = 0.03 favours NBO	MMSE used symptoms/unblinded assessment at 3 days to decide second course of 3 treatments 3/5 HBO patients with DNS identified after study finished

5.3.3. Delayed neurological sequelae

Table 5.4 summarises prospective comparative and randomized controlled trial outcome data for DNS, as defined above. Delayed neurological sequelae represents a biphasic clinical pattern after CO poisoning, where patients experience improvement with acute treatment, then a delayed deterioration in their neurological and cognitive function. These patients constitute the group who are "abnormal", then "normal", then deteriorate again.

Delayed neurological sequelae occur between 3 - 40 days after the CO exposure, frequently after apparent recovery from the acute event (Choi 1983, Mathieu et al 1985, Myers et al 1985, Goulon et al 1986, Min 1986, Thom et al 1995). Studies using cognitive testing have demonstrated neuropsychological relapse rates of between 12 and 23 percent for treatment with NBO (Choi 1983, Mathieu et al 1985, Myers et al 1985, Min 1986, Thom et al 1995). The occurrence of DNS doesn't correlate with COHb levels, and cognitive function deterioration has been reported even with mild CO poisoning (Mathieu et al 1985, Thom et al 1995). Headaches, difficulty concentrating, memory deficits and mood irritability are associated with objectively demonstrable deficits in cognition and balance (Myers et al 1985). In more severe cases, a Korsakoff - like syndrome may ensue, and ataxia, incontinence and Parkinsonism rigidity. This deterioration has been partly reversible without treatment in some series (Mathieu et al 1985, Weaver et al 1996[2]). However it may be progressive with patients experiencing significant deterioration in their neurological and cognitive function (Smith and Brandon 1973). At 3-year follow-up, in Smith and Brandon's study, 10.8% of these patients had gross neurological and cognitive defects, and a further 38.5% of patients had memory deficits. When discharged from hospital three years earlier only 2.2% of 206 survivors of CO poisoning had demonstrable abnormalities of neuropsychiatric functions.

More severe DNS occurs in the elderly (Choi 1983, Min 1986, Goulon et al 1986, Thom and Keim 1989). Smith and Brandon (1973) associated DNS with increasing age and severity of acute neurological toxicity. Goulon et al (1986) also noted that DNS occurred more frequently in individuals' aged > 50 years and those treated > 6H after poisoning. Individuals with longer exposures to CO were at higher risk of DNS (Goulon et al 1986). It has been suggested that inadequate treatment resulting in persistent CO and delayed excretion from body stores may be a reason for DNS (Myers et al 1985). Willms et al demonstrated offgassing of CO in patient's breath even when COHb had returned to normal but they did not correlate this with patient outcomes. Scheinkestel et al's data

however, does not support inadequate treatment as a cause of DNS (Scheinkestel et al 1999). They reported 5/191 (2.6%) of their patients developed DNS, despite using an prolonged oxygen treatment regimen that would have removed all CO from their patients. This suggests that DNS may result from causes other than direct CO toxicity. No studies have attempted to correlate treatment duration, or treatment endpoint with the risk of DNS.

The natural history of the DNS is variable. Milder syndromes tend to recover spontaneously, however, individuals may suffer incapacity from poor concentration, headaches, memory deficits, fatigue, dizziness, ataxia and confusion for up to 11 weeks (Thom et al 1995). In Thom's study, four out of 7 patients with DNS were able to continue with their normal activities despite their symptoms and cognitive impairment. Three were incapacitated due to headaches, fatigue and difficulty concentrating. One had a significant intention tremor. Thom et al's study supported data from other authors: the mean age of patients with DNS was 46 years compared with 37 years for those who remained well. Older patients with DNS took significantly longer to recover from their DNS (Mean 59 days compared with mean 29.7 days for the younger patients).

The largest series of DNS originate from Korea. Choi (1983) reported the clinical findings in 549 admitted patients (542 with LOC) from a series of 2360 patients with CO poisoning (1976 - 1981) who presented to the Severance Hospital. Of the 549 patients, 65 developed DNS. The symptom-free period before onset of DNS had a range of 2 to 40 days (mean 22.4 days). Min (1986) expanded upon Choi's data, with 738 admissions from 2967 presentations (1976 - 1984), from which 86 developed DNS (12%). Min's series demonstrated severe neuropsychiatric abnormalities, with the most frequent being apathy, disorientation, and amnesia (100%), urinary or faecal incontinence (93%), 95% hypokinesia (95%), mutism (95%), positive glabellar sign (91%), gait disturbance (91%), grasp reflex (87%), increased muscle tone (86%), and irritability (76%). Of 167 patients aged 60-79, 57 (34%) developed DNS. Fifty six of these older patients were followed to one year, and thirty four had improved enough to manage their usual daily activities. The other 22 older patients had deficits ranging from residual weakness and memory impairment to Parkinsonism and paralysis; six died during their hospital admissions. Only 7 of 451 patients (2%) under the age of 40 developed DNS. Min (1986) was unable to find any correlation between EEG, CT findings and the development of DNS. Min stated that hyperbaric oxygenation did not prevent the development of DNS, but did not provide numerators or denominators for risk of DNS versus the treatment administered, nor at what

time the patients received HBO. Neither of the Korean authors provided details of the oxygen dose or method of oxygen administration used to treat DNS, and COHb levels were not documented.

Hyperbaric oxygen has been effective in reversing delayed relapses after apparent recovery from CO poisoning (Myers et al 1981, Myers et al 1985, Gibson et al 1991), even when applied at 3 months post exposure (Mitani and Yagi 1997). In the study by Myers and co-workers, hyperbaric oxygen had two beneficial effects. There was a reduction of delayed sequelae after initial treatment with HBO, and HBO was effective in reversing the effects of delayed relapses with milder clinical syndromes who had initially been treated with NBO. HBO has also been successful in preventing DNS. In a prospective randomized trial, Thom et al (1995) found a statistically significant reduction of DNS in those treated with HBO compared with those treated with NBO. Thom's group used unblinded psychometric testing to measure outcome.

Gorman et al (1992) reported 100 consecutive admissions to the Royal Adelaide Hospital, and evaluated outcome using psychometric testing. They found that 25% of the group treated with NBO had PNS at follow-up, and 25% experienced DNS. In the group receiving one HBO treatment, 38% had PNS and 8% suffered DNS. With multiple HBO treatments, there were 18 percent with PNS and none with DNS. In this series, DNS manifested as of loss of higher mental functions, depression, motor disorders, visual disturbances, and urinary incontinence, that were not present at discharge from hospital.

Additional aims of my thesis were to prospectively enrol a case series of CO poisoned patients to document their clinical and demographic characteristics and to assess if any of these were associated with the outcomes of DNS and PNS at 3 months. I also aimed to identify the factors that influence CO load (measured by ECO) in poisoned patients including the duration and intent of exposure, the source of CO, the delay to initial oxygen treatment and study entry, and the neurological status on arrival in the ED.

5.4. Treatment of CO poisoning

Oxygen is known to be an antidote to CO poisoning. It has been known since Haldane's experiments in 1895 that the toxic effects of CO can be offset by hyperbaric oxygen. He found that a mouse exposed to one atmosphere of CO in 2 ATA of oxygen (total pressure 3 ATA) showed no toxic effects from the CO (Haldane 1895). The mouse met its metabolic demands for oxygen by utilising the greatly elevated dissolved oxygen in the plasma. Human studies of the treatment of carbon monoxide poisoning have focussed on delivery of oxygen at one atmosphere (NBO), or at elevated pressure (HBO).

5.4.1. Oxygen dose

There is evidence from comparative studies and controlled trials that delays greater than 6 hours in administering NBO therapy may cause higher levels of morbidity and mortality (Goulon et al 1986, Raphael 1989, Thom et al 1995). A review by Weaver in 1999 concluded "*Presently critical review of the literature regarding acute CO poisoning indicates that 100% O2 is the clinical standard*" (Weaver 1999). Eight comparative and randomized studies have precisely documented oxygen dose administered during treatment (Mathieu et al 1985, Raphael et al 1989, Gorman et al 1992, Ducasse et al 1995, Thom et al 1995, Mathieu et al 1998, Scheinkestel et al 1999, Weaver et al 2002). When comparing the six randomized studies, variations in oxygen doses are apparent, summarised in table 5.5.

Table 5.5 Oxygen dose delivered to each treatment group for the six RCT's.

Author (year)	HBO Dose (Atmosphere.hours)	NBO Dose (Atmosphere.hours)
Raphael et al 1989	8.0	6.0
Ducasse et al 1995	12.0	9.0
Thom et al 1995	4.4	?
Mathieu et al 1998	4.6	12.0
Scheinkestel et al 1999	80.5	72.0
Weaver et al 2002	13.4	6.5

The oxygen doses in table 5.5 have been derived from information supplied in the papers. By definition, one atmosphere – hour equals 100% oxygen delivered for 1 hour at 1 ATA. It is apparent that in many of the studies, the oxygen doses are different in the two treatment arms. Applying COHb elimination data, there is no question that HBO removes CO from the body faster than NBO. However

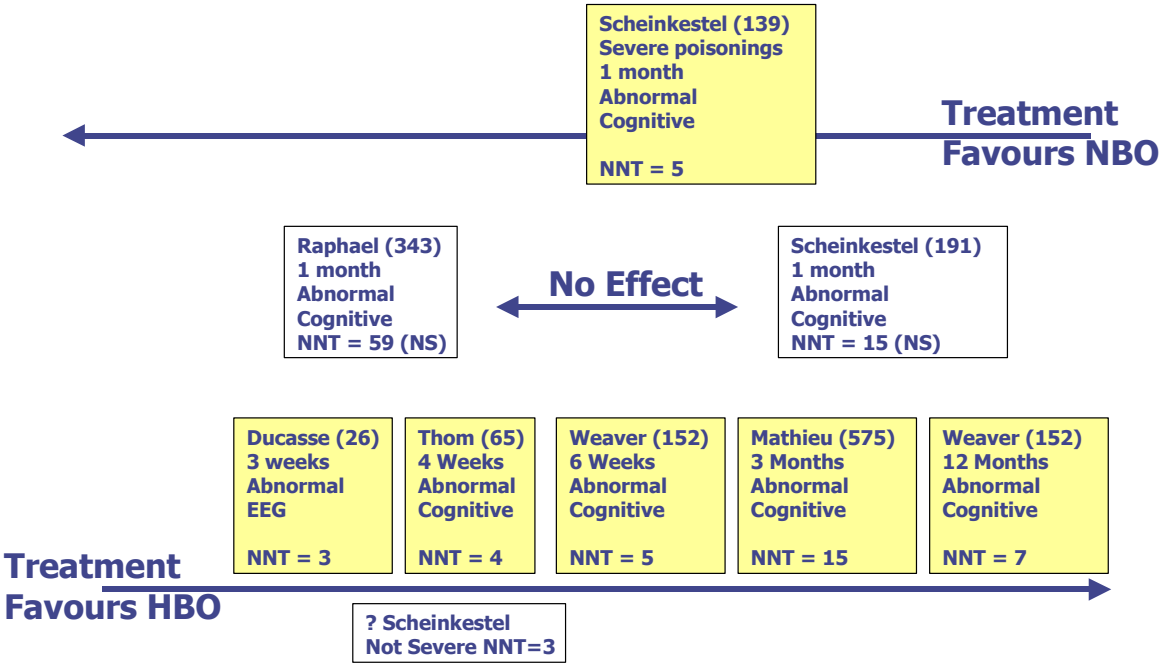
the optimum dose of oxygen required for treatment CO poisoning is still not clear, and may partly stem from the observation that a clear end-point for treatment has not been defined (Van Meter et al 1994, Olson and Segar 1995). Whether or not 100% oxygen as opposed to delivery of high flow oxygen by non-rebreather face-mask, makes a difference to outcomes in CO poisoning remains unknown.

Pace et al (1950) first identified the goals of treatment of CO poisoning as resuscitation, treatment of hypoxia, and elimination of CO: "*Hence in treatment of CO poisoning, where not only resuscitation of the victim but avoidance of serious and permanent after effects of prolonged hypoxia is also important, the further increase in CO elimination rate by administration of O_2 under high pressure seems of considerable practical value*". Paces group also stated "*Clinical trial of high pressure oxygen as a means of therapeusis in CO poisoning therefore appears warranted, and is recommended where suitable pressure chamber facilities are available*." Over 50 years of research has been conducted and the ideal treatment for CO poisoning is yet to be resolved.

5.4.2. Summary of clinical trial data

Figure 5.3 summarises results from six randomized controlled trials (RCT's) comparing HBO with NBO for the treatment of CO poisoning, described in tables 5.3 and 5.4 (Raphael et al 1989, Thom et al 1995, Ducasse et al 1995, Mathieu et al 1998, Scheinkestel et al 1999, Weaver et al 2002).

Figure 5.3 Treatment outcomes for six RCT's comparing NBO with HBO



There are methodological differences in all of the RCT's comparing NBO with HBO that have been undertaken at this point in time, that make it difficult to compare outcomes. Some of these were documented in tables 5.1 to 5.4. All of the RCT's had different entry criteria in relation to time between rescue and treatment, and included different levels of severity of CO poisoning. The best-designed trials to date were conducted by Scheinkestel et al (1999) and Weaver et al (2002). Both used detailed psychometric tests to assess outcomes. A Cochrane review by Juurlink et al (2005) concluded that "Existing randomized trials do not establish whether the administration of HBO to patients with carbon monoxide poisoning reduces the incidence of adverse neurological outcomes. Additional research is needed to better define the role, if any, of HBO in the treatment of patients with carbon monoxide poisoning. The research question is ideally suited to a multi-centre randomized controlled trial."

5.4.3. Defining treatment end-point

Over the last two decades, comparative and randomized trials for treatment of CO poisoning have compared outcomes for NBO treatment versus HBO treatment (Myers et al 1985, Raphael et al 1989, Gorman et al 1992, Ducasse et al 1995, Thom et al 1995, Mathieu et al 1998, Scheinkestel et al 1999, Weaver et al 2002). None of the trials allocated patients to "air only" treatment. In the above comparative and randomized trials, only Myers' group titrated treatment to a physiological end-point (COHb < 5%). Gorman's group provided one, two or more hyperbaric oxygen treatments based on the condition of the patient. All other authors used fixed doses of oxygen or HBO in accordance with a protocol. Apart from pathophysiological data demonstrating more rapid COHb clearance with increasing P_IO_2, there is no proof that oxygen therapy (compared with air), is beneficial in CO poisoning (Pace et al 1950, Peterson and Stewart 1970, Wagner 1975, Myers et al 1984, Levasseur et al 1996, Jay and McKindley 1997, Weaver et al 2000). To date no studies have identified a physiological end-point, or an end-point based on the clinical condition of the patient that might be useful in guiding the treatment of CO poisoning.

Despite their validity in measurement of outcome, psychometric tests have limited value in determining treatment end-point in acute CO poisoning, due to co-ingestions, coma and possible lead times between treatment and clinical recovery. Thom and colleagues used an end-point to treatment that was subjective - the resolution of all symptoms (Thom et al 1995). Raphael et al (1989), Mathieu et al (1998), Scheinkestel et al (1999), and Weaver et al (2002) used completely different predefined

treatment schedules, and did not titrate to any specific clinical endpoint. Empirical treatment schedules may over-treat some individuals and under-treat others. Scheinkestel et al (1999) treated all patients for 3 days on high-flow oxygen, and may have caused oxygen toxicity in their HBO treatment arm.

A more effective method is required to assess CO in body stores and also to assess the removal of CO from the body during treatment. Ideally, a treatment schedule would be tailored to the needs of the individual, based on their degree of poisoning. This has been attempted in the past using COHb as a marker. Myers et al (1985) treated all patients until their COHb levels were <5%, in an attempt to tailor treatment to the needs of the patient. This end-point may have under-treated the NBO group, resulting in a 12% incidence of DNS in that group. There have been no studies measuring clinical outcomes when patients were treated to a level of unrecordable COHb, hence removal of all CO is unproven as a treatment end-point. It is logical to use the final pathway for CO excretion from the body (the lungs), to titrate treatment end-point. From limited available evidence, CO reaches unrecordable levels later than the COHb (Willms et al 1985). Expired CO may be a more sensitive indicator of CO stores in the body, and perhaps be useful as a guide to treatment end-point. This would allow treatment to be tailored to the individual needs of each patient.

Hence in this thesis a further aim was to determine if unrecordable ECO might complement other methods to guide treatment end-point, by correlating post-treatment neurological status with clinical outcomes assessed at three-month follow-up using neurological and cognitive testing. As the proposed study was not randomized, a definitive answer to this question was not possible.

5.5. Unresolved issues

There are a number of unresolved issues relating to CO poisoning based on the review of the literature.

(1) No studies have identified a reliable marker of acute CO poisoning severity, which correlates with patient outcomes after treatment.

(2) There is considerable debate concerning the appropriate oxygen dose to use in the treatment of CO poisoning (Raphael et al 1989, Gorman et al 1992, Tibbles and Perrotta 1994, Thom et al 1995, Ducasse et al 1995, Mathieu et al 1998, Scheinkestel et al 1999, Weaver et al 2002).

(3) Available trials have used many different fixed-dose empirical treatment of CO poisoning, or titrated to a possibly inadequate end-point of < 5% COHb (Myers et al 1985, Raphael et al 1989, Gorman et al 1992, Tibbles and Perrotta 1994, Thom et al 1995, Ducasse et al 1995, Mathieu et al 1998, Scheinkestel et al 1999, Weaver et al 2002).

(4) Measurement of outcome has also attracted significant debate in the literature, and there is now broad agreement that cognitive testing should form part of the outcome assessment. Cognitive testing should be conducted at discharge, one month and least three months after acute treatment, to ensure that cases of DNS are not missed. However, the relationship between patient symptoms, cognitive function abnormalities, and daily living functional status is yet to be defined.

It should be possible to further investigate CO at its end-point of excretion from the body – via the breath. Measurement of ECO is non-invasive, and ECO sampling has the potential to compliment existing methods of monitoring the CO poisoned patient, during acute treatment. In order to research CO elimination via the breath (CO offgassing), it will be necessary to produce an apparatus capable of measuring ECO in the breath. This should be possible from existing devices. With continuous ECO monitoring using this new technology, it might be possible to quantify CO elimination from the body, and validate the phenomenon of CO offgassing in human subjects. Measurement of ECO may be useful in the diagnosis and determining treatment end-point for CO poisoning. This may allow treatment to be tailored to the individual needs of each patient. Acute ECO measurement would also need to be compared to post-treatment neurological and cognitive function, to assess its utility as an acute marker of CO poisoning. Expired CO has not been previously investigated in detail in the literature, and it may compliment existing methods to guide acute treatment of CO poisoning.

Available randomized and comparative studies of the treatment of CO poisoning have some variability in the definition of normobaric oxygen, and none recorded the oxygen concentration**.** Most of the high

flow oxygen systems would not allow collection of exhaled gas from the patients because they were open to the environment. This was a practical consideration for my research in collecting exhaled breath samples. In addition, not knowing the treatment oxygen concentration could act as a confounder for my research, because it would affect CO elimination, and there would be variation in delivered oxygen concentration between individuals. In my proposed research, this uncertainty will be removed by integrating the ECO measuring equipment to an oxygen analyser, to confirm that patients are receiving 100% oxygen.

6. DEVELOPMENT AND EVALUATION OF THE EXPIRED CO APPARATUS

This chapter will cover the practical issues of developing an apparatus for measuring ECO, and its clinical application. Evaluation of the apparatus for measurement of ECO will be covered in subsequent chapters.

6.1. Aim

To design and construct a portable apparatus to measure CO in the exhaled breath that was suitable for clinical sampling of ECO from subjects breathing air, 100% oxygen and hyperbaric oxygen.

6.2. Methods

To meet the needs of the study, the ECO apparatus was required to:

1. Measure CO concentration in real-time
2. Measure exhaled respiratory minute volume
3. Measure oxygen concentration in real-time

These measurements would permit the calculation of the *concentration* of ECO as well as the *quantity of CO offgassed*, when applied in the clinical setting. As described in the literature review, measurement of oxygen concentration was essential to *validate the oxygen dose* delivered. Each of the components of the apparatus will be described individually.

6.2.1. Desirable features of a CO analyser

Before undertaking the study, the features of the ideal apparatus for measuring ECO were defined. The required features are summarised below:

(1) An ability to detect CO in the ambient atmosphere with a lower limit of detection of 1 ppm.

(2) An operating range of the apparatus of 0 - 500 ppm CO, to cover more than the expected ECO levels in poisoned patients.

(3) The advantage of real-time recording for the duration of the treatment.

(4) A portable robust and well-constructed battery operated unit to enable its transport to subjects.

(5) An easily accessible sampling port to permit attachment of gas tubing in the exhalation circuit from the patient.

(6) A simple to use apparatus, requiring minimal training.

(7) Rapid response to changing concentrations of CO – (90% response in less than 1 second) to permit real-time measurement of ECO.

(8) Minimal interference from other gases including water vapour.

(9) Low Cost.

(10) Ability to perform under hyperbaric conditions

A Dräger® 190 Datalogger portable CO detector (Dräger Incorporated, Pittsburgh, Philadelphia, USA, figure 6.1) was selected because it satisfied the requirements for the project outlined above. These features included:

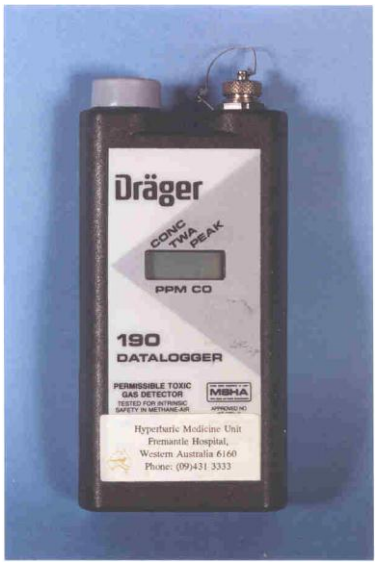
- It was portable (12.5cm x 7cm x 3 cm), and robust as it had been designed for measurement of CO in the ambient environment of working firemen.
- The unit used an electrochemical sensor system (described below), capable of real-time CO readings, to an accuracy of 1 ppm in the range of 1 - 200 ppm, and 5 ppm in the range of 200 - 1000 ppm (Accuracy ± 1% in lower range, and ± 3% in higher range).
- An additional feature was its ability to store CO readings over a 12-hour period and download them into a computer.
- The sensor port was able to be connected to standard breathing tubing for analysis of the gas.
- The sensor was programmed to recalculate CO levels every 500 msec and was capable of recovering for re-use within one minute of an exposure to 5000 ppm CO.
- It fell within the allocated budget of $1200.

- **Minimal interference in the presence of other gases including:**

  water vapour, methane, hydrogen sulphide, ethane, nitrogen dioxide, ethylene, nitric oxide, propane, sulphur dioxide, benzene, carbon dioxide, nitrogen, oxygen and ethanol. (National Dräger Incorporated, 1989)

The only gas which was found to influence the unit was hydrogen (H_2); at a concentration of 1000 ppm, the data logger recorded a value of CO = 90 ppm. This was considered not to be a problem in the hospital setting.

Figure 6.1 Dräger® 190 Datalogger



The Dräger® 190 Datalogger used an electrochemical system for detecting CO. The gas sample (expired breath) diffused through a membrane into an acidic liquid electrolyte in the sensor. The electrolyte contained a sensing electrode (anode), a counter electrode (cathode), and a reference electrode. An electronic potentiostat-circuit ensured a constant electronic voltage between the sensing electrode and reference electrode. The voltage, electrolyte and electrode material were selected by Dräger Corporation to suit the CO gas. The voltage of the system was set so that the CO contained in the sampling air was oxidised electrochemically at the sensing electrode, and this reaction generated electron flow. The flow of electrons was in direct proportion to the CO concentration, and 1mV was

equal to 1 ppm. At the same time, oxygen from the sample reacted with the counter electrode electrochemically. The chemical reactions were as follows:

Chemical reactions:

Sensing electrode: $CO + H_2O \rightarrow CO_2 + 2H^+ + 2e^-$

Counter Electrode $\frac{1}{2}O_2 + 2H^+ + 2e^- \rightarrow H_2O$

An independent assessment of the Dräger® 190 Datalogger demonstrated a linear response to increasing CO concentrations (range 1 to 50 ppm), and confirmed the manufacturers stated accuracy of ±2ppm or ±3%, whichever is greater (Kronmiller and Mulik 1991). This accuracy was found to be independent of humidity and temperature variations. There was no interference from sulphur dioxide or nitric oxide. The 190 Datalogger had been designed for ambient air readings at 1ATA in a high CO environment. This was considered to be an advantage for its use as a clinical tool in assessing CO poisoning. Thus the Dräger® 190 Datalogger satisfied the study requirements for clinical CO sampling. We chose not to further test its accuracy for measuring CO levels, relying on regular calibration according to manufacturer's guidelines. The apparatus was set to zero using a CO free gas (pure nitrogen), and a reference gas containing 150 ppm CO was used to set the gain, on a weekly basis.

6.2.2. Measurement of oxygen concentration

In addition to measuring CO, it was necessary to measure the oxygen concentration in the expired gas passing through the CO analyser. This was to confirm that the treatment was standardised and 100% oxygen was delivered to the patients. A Hudson Oxygen analyser was already available at the Diving and Hyperbaric Medicine Unit (Hudson RSI Corporation, Temecula, California, USA – Figure 6.2). The battery operated Hudson Oxygen analyser used a galvanic micro-fuel cell sensor to generate a current in proportion to the oxygen concentration. This cell consisted of an electrochemical cell with two electrodes (silver and lead) in contact with potassium hydroxide. The oxygen diffused through a Teflon® membrane and in contact with the silver cathode, was reduced to hydroxyl ions. The hydroxyl ions then flowed towards the lead anode to be oxidised. The overall reaction produced a current that was proportional to the rate of consumption of oxygen, and the oxygen concentration. It had a meter that showed oxygen concentration in real-time, and was stated by the manufacturer to have an absolute

accuracy of ± 2% O_2 concentration. The response time was not stated, however, given that it was able to produce a continuous current in proportion to oxygen concentration, it was sufficiently rapid for real-time recording. The chemical reactions are as follows:

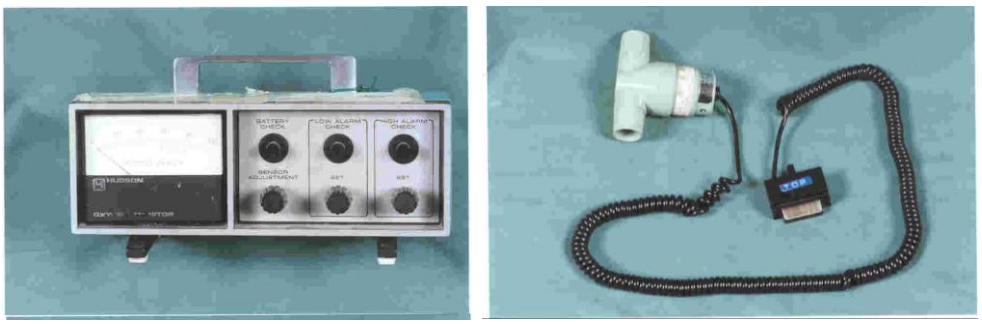
Cathode (Silver) $O_2 + 2H_2O + 4e^- \rightarrow 4OH^-$

Anode (Lead) $2Pb + 6OH^- \rightarrow 2PbO_2H^- + 2H_2O + 4e^-$

Overall $O_2 + 2Pb + 2OH^- \rightarrow 2PbO_2H^-$

The consumption of oxygen of the micro fuel cell was less than 100 millilitres per minute, which was only 1% of the expected patients' RMV of >10 LPM. The apparatus was calibrated using zero Oxygen (100% nitrogen), and 100% oxygen on a weekly basis.

Figure 6.2 Hudson oxygen analyser and sensor



The apparatus was stated by the manufacturer to provide accurate oxygen percentages in the humidity range of 0-99%. For subjects breathing 100% oxygen, allowing for variability in exhaled water vapour and CO_2, the expected exhaled oxygen concentration breathing NBO was 89-95%, and breathing HBO at 2.8ATA, this was 96-98% (West 2000). In practice, if measured exhaled oxygen concentration fell below 90 - 95%, then a leak in the circuit was suspected and investigated.

6.2.3. Measurement of respiratory minute volume

In order to quantify the volume of CO excreted, it was necessary to measure the volume of gas exhaled by the patient; [CO] in ppm x RMV (L/min) x 1000 ml/L = volume CO expired (mL/min). This was undertaken using a Bourns® LS75 ventilation Monitor (Bourns Life Systems, California USA). A photograph of this unit is shown in Figure 6.3. The Bourns® ventilation monitor was a solid state medical calculator that automatically measured flow without the use of moving parts. The flow sensor operated on a vortex principle, in which the air stream of the patient's exhaled gas was directed past a

rod. This created flow vortices, which were detected by an ultrasonic beam. The ultrasonic beam was generated by a crystal transducer. The vibrating air stream intermittently changed the ultrasonic beam strength, the variations were detected by a second crystal and counted into an electrical signal proportional to flow. Its overall accuracy was stated to be ± 5% over a range of 0 to 99.99 LPM, with a respiratory rate up to 60/minute. Minute volumes were obtained by summing all of the tidal volumes over a one-minute period. The vortex concept was stated by the manufacturer not to be affected by gas density, gas stream composition, temperature or humidity. All measurements were obtained at one atmosphere absolute pressure. For individuals treated with HBO, the exhaled gas was channelled outside the chamber via an "overboard dump".

Figure 6.3 Bourns® LS75 Ventilation Monitor

6.2.4. Apparatus calibration

The apparatus for measuring CO and oxygen concentrations were calibrated on a weekly basis in accordance with the schedules described above. The ventilation monitor was calibrated weekly using a standard one-litre calibration syringe. If discrepancies were noted in zero baselines for the 190 Datalogger, it was forwarded to Dräger Australia, Kewdale WA, for factory calibration. If discrepancies were noted in the calibration of the oxygen analyser or ventilation monitor, they were forwarded to the supplier, Anaesthetic Supplies Pty Ltd, Bayswater WA, for factory calibration and/or replacement of parts. In practice, factory support was required only once for each apparatus, during the study period. This did not interfere with data collection.

6.2.5. The complete ECO measuring apparatus

Connecting the Bourns® ventilation monitor in series with the CO and Oxygen analysers, enabled measurement of the subjects' RMV at the time ECO and O_2 measurements were recorded. The complete apparatus is shown in Figure 6.4. The system had one-way valves connected to the breathing circuit to ensure there was unidirectional flow and no rebreathing. The apparatus was attached to a portable tray, and was able to obtain samples from individuals breathing air or 100% oxygen at 1 ATA, or from the hyperbaric environment, via the exhaled breath sampling port. Portability was essential when samples were to be taken from emergency patients. All three units were battery operated. Given the relatively slow response times of 0.5 to 1 second for the CO and O_2 analysers, true end-tidal readings could not be measured. The apparatus was therefore capable of measuring mean ECO and O_2 readings. As stated in the literature review the mean ECO was expected to be lower than true EtCO because the latter is a peak value reflecting alveolar CO concentration. Mean ECO values were expected to be 20 – 35% less than EtCO, however direct comparison was not possible in this study.

Figure 6.4 ECO Apparatus Showing Exhaled Breath Sampling Port

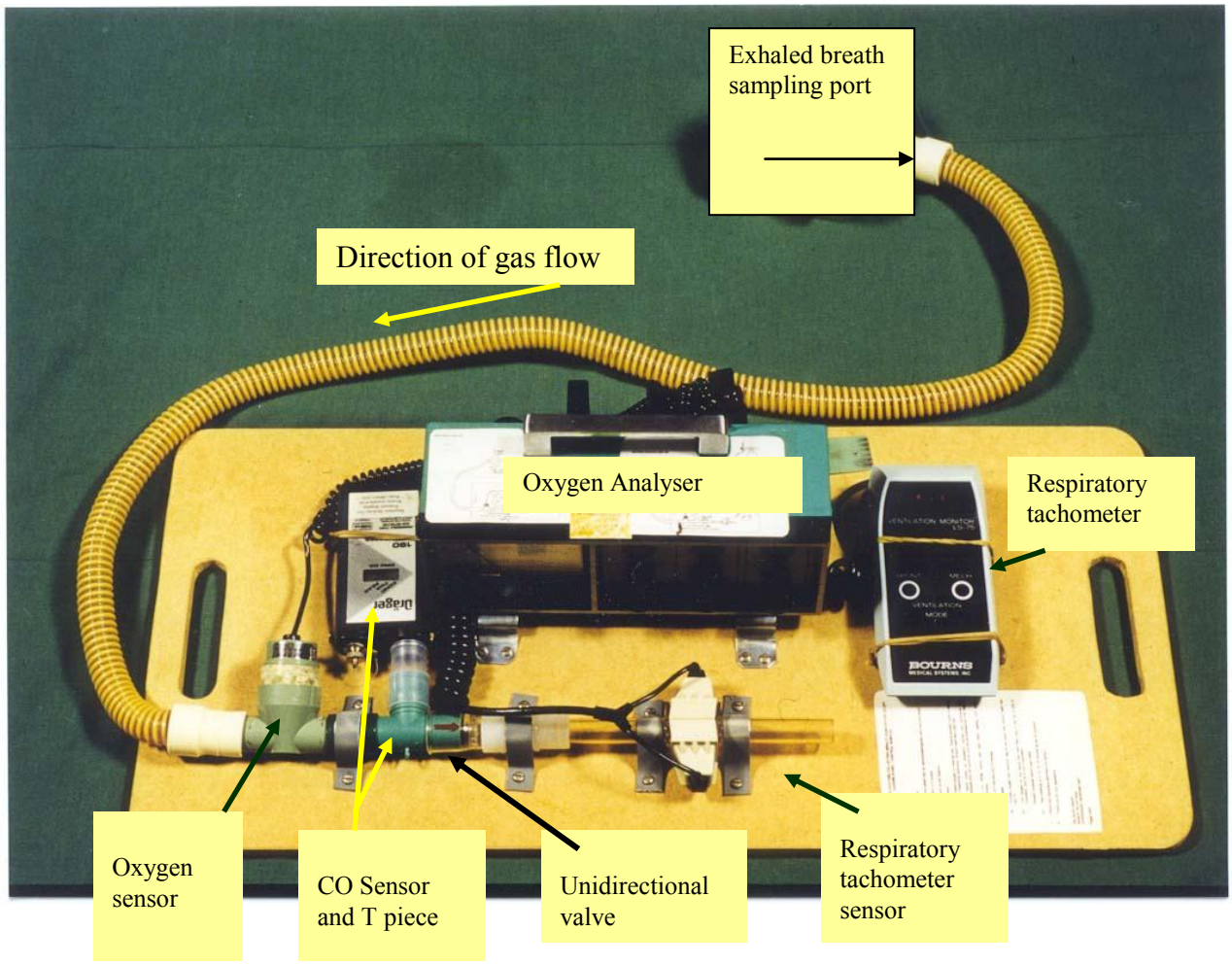
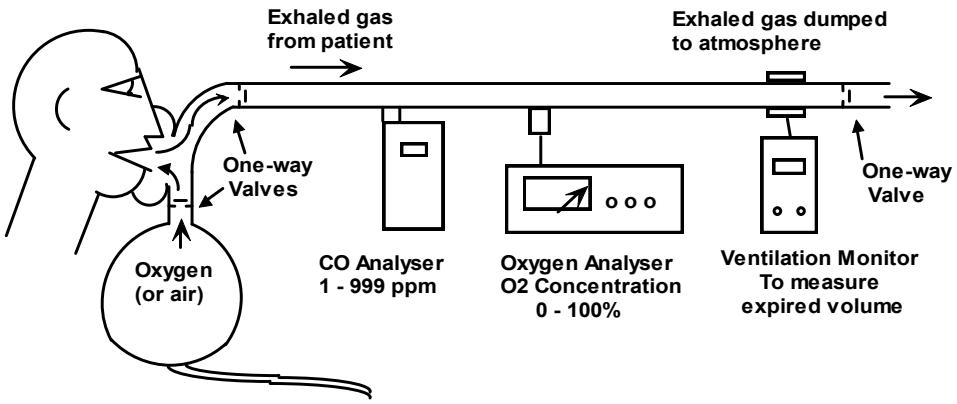


Figure 6.5 Schematic diagram of the ECO apparatus



6.2.6. ECO sampling from subjects breathing air, NBO and HBO

Figure 6.4 showed how the ECO apparatus was arranged on a portable tray for transport to the patients, and figure 6.5 provides a schematic diagram of the apparatus connected to a subject with a face mask. The apparatus was configured to allow sampling (all at 1ATA) from subjects breathing air, 100% oxygen and HBO (spontaneously breathing and ventilated). This will be described below.

Sampling from Subjects Breathing Air and NBO

The mask was strapped to the patient, to ensure an air-tight fit. Subjects received 100% oxygen at 1 ATA via a reservoir system consisting of a 3-litre reservoir bag and face-mask (shown in figure 6.5). When supplying 100% oxygen. Oxygen delivery was matched to the patient's RMV, by careful titration of the flow rate, so that the reservoir bag was completely full at the commencement of each inspiration, and partly full at the end of expiration. To deliver air, the oxygen supply and reservoir bag was removed, allowing air entrainment from the atmosphere via the entry valve. The exit limb of the circuit was easily connected to the ECO apparatus (figure 6.4.). Exhaled gas was then analysed from the individual. Because of one-way valves, there was minimal rebreathing, and the circuit could be used for all ages (including paediatric, with appropriate oxygen delivery systems). The apparatus then measured mean ECO concentration, oxygen concentration and volume in real-time.

The tubing of the ECO apparatus could also be connected to the expiratory limb of a mechanical ventilator or Laerdal® bag for measurement of CO, O_2 concentration and minute volume in the exhaled breath of ventilated patients, either at one atmosphere, or from outside the hyperbaric environment, via the overboard dump.

Sampling from patients treated with HBO

Modifications to the hyperbaric chamber were required in order to measure exhaled breath samples from patients receiving hyperbaric oxygen treatments. The expiratory limb of the patient's built in breathing set (BIBS) (Scott USA) was connected to a specially modified one-way pressure reduction regulator and chamber penetrator (collectively termed "overboard dump") to channel the exhaled gas from inside to outside the hyperbaric chamber. This circuit was a continuous pipe from the patient to the research apparatus, with one way valves to ensure no backflow occurred. A one-way valve was also on the efferent side of the CO and oxygen analysers, to prevent dilution from backflow. All ECO measurements from patients treated with HBO then took place at 1ATA, *outside* the hyperbaric

chamber, after the patients exhaled breath has been depressurised and expanded in volume by a factor of 2.8. The one-way pressure reduction regulator was triggered only when the patient exhaled, causing exhaled gas to be directed into the overboard dump. The external overboard dump on the hyperbaric chamber is shown in figure 6.6. This was independent of the usual gas scavenging Venturi system, and dedicated solely to the research subject. It did not affect the patient's exhalation breathing resistance because of the large pressure differential from the inside to the outside of the chamber (2.8 ATA versus 1.0 ATA). Formal measurements of the expiratory resistance and exhalation trigger pressure of the breathing circuit were not undertaken. Because there was a reduction in ambient pressure from inside the hyperbaric chamber to outside, measurement of sample volume was undertaken at 1ATA. This allowed CO elimination during treatment with hyperbaric oxygen to be compared with measurements taken at during treatment with NBO and air, at 1ATA, but clearly with the expectation that greater volumes would be measured from HBO samples, because they had expanded by a factor of 2.8 coming out of the chamber.

The CO offgassing apparatus was in continuous communication with the patient, however, recording of [CO], [O_2] and RMV took place at 5-minute intervals. During depressurisation of the chamber, final hyperbaric samples were recorded from the subject at 1.5 ATA pressure. The expiratory limb of the BIBS apparatus was then connected to the normal Venturi scavenging system to prevent build-up of any breathing resistance as the pressure differential between inside and outside of the chamber became less. This was normal practice during depressurization. The time taken to depressurize from 1.5 ATA to 1 ATA was just over 8 minutes, and the extra 3 minutes before obtaining the 1ATA sample was not considered to be significant. Final samples were then collected at 1ATA upon the patient's exit from the hyperbaric chamber.

Figure 6.6 External "Overboard Dump" for Sampling ECO from subjects in the Hyperbaric Environment (Red Tap and Brown Corrugated Tubing)

6.3. Discussion

The goal of developing an apparatus suitable for measuring mean carbon monoxide levels in the exhaled breath was successfully achieved (figure 6.4). A description of practical issues regarding use of the apparatus is outlined in this discussion. More detailed evaluation using volunteers and patients is described in chapters 7 to 15. The accuracy of the apparatus (its ability to measure CO concentration, oxygen concentration and respiratory minute volume) was not formally evaluated, however we relied upon regular calibration (as described above) to ensure its operational capability.

Because of its portability, it could be taken to the patient as they initially presented, and moved with them as they were transferred for definitive treatment. Continuous measurement of oxygen concentration in the exhaled gas was found to be an advantage; permitting real-time feedback when the treatment O_2 concentration fell below 90 - 95%. This alerted the treating doctor, and enabled immediate correction of the problem, for example, a leaking mask, or other cause. It also ensured standardisation of the 100% oxygen treatments.

The apparatus was easily connected to the exit limb of the breathing apparatus for patients and controls. Control data was successfully collected from 213 volunteers with ages ranging from 9 to 75. (37 were children $\leq$ 14 years). The control sample data is described in detail in chapter 7. Samples were later obtained from 66 acutely poisoned ED patients (including five who were intubated and ventilated). These are described in chapters 8 to 15.

Some practical limitations were identified. No air entrainment was available for the 100% oxygen mask system, if the oxygen supply failed. However, this did not prove to be a problem, because all controls and patients received close clinical supervision, and on the one occasion where oxygen supply was briefly interrupted, staff quickly connected the patient to a fresh oxygen source. This problem was not directly due to the CO offgassing apparatus, but more a safety issue with NBO treatment. Patients who remained unconscious were usually intubated, and received manual ventilation via a Mapleson B circuit, Laerdal ® resuscitator circuit, or via a Dräger® Oxylog ventilator. Humidification of oxygen was not undertaken during the study. For supply of oxygen over periods longer than 6 hours, humidification is desirable. Acutely poisoned patients noted airway dryness when breathing from the circuit at 1 ATA for periods greater than 6 hours. This was not a problem for those treated with hyperbaric oxygen, because they had shorter treatment times.

It was not possible to compare the physical setup of the ECO apparatus with those used by other authors in previous studies. Willms and co-workers did not describe their apparatus in the 1985 report (Willms et al 1985). A pilot study by Langston and co-workers (1992) used a Dräger® PAC 11 CO monitor in series with an apparatus for measuring RMV. Mathieu and colleagues (1999) did not describe their apparatus. Oxygen concentrations were not measured by Langston's or Mathieu's groups. Because the CO offgassing apparatus measured exhaled oxygen concentration, this research will be able to confirm that 100% oxygen treatment was reliably delivered. The apparatus proved suitable for its use in the clinical setting, and satisfied all of the criteria for conducting the proposed research.

6.4. Conclusions

A low cost, portable and robust apparatus was successfully developed for measurement of ECO, O_2 concentration and minute volume. The ECO apparatus was suitable for use in a variety of clinical settings with patients inhaling dry air or oxygen. It was portable enough to be taken to the subject's bedside in the acute setting. Clinical use of the apparatus to measure mean ECO and CO elimination in adults and children breathing air and NBO, HBO and ventilated patients will be described in chapters 7 to 15.

7. CLINICAL EVALUATION OF THE CO OFFGASSING APPARATUS IN HEALTHY NON-SMOKERS, SMOKERS AND DIVERS EXPOSED TO PRESSURE

Introduction

This chapter investigates the utility of the apparatus as a clinical tool for measuring ECO in non-poisoned human subjects. The purpose of collecting control samples was to obtain raw data on the levels of ECO in individuals not exposed to CO, and also to examine the effect of cigarette smoking (a known source of CO). There was little previous work to compare with, because the concept of measuring ECO was novel.

7.1. Aims

1. To quantify mean ECO in healthy non-smoking volunteers breathing air
2. To determine mean ECO levels in smoker controls breathing air and 100% oxygen
3. To investigate the relationship between mean ECO and smoking habit
4. To determine the effect of pressure on mean ECO in a population of healthy divers breathing air, 100% oxygen and HBO

7.2. Methods

7.2.1. Recruitment of controls

Measurement of ECO from non-smoker and smoker controls took place while breathing air and NBO at 1ATA pressure. The main area of interest was the ECO values in non-smokers and smokers. Hence measurement of RMV and CO offgassing was not undertaken, because the control population was not being treated to remove CO. Expired CO levels were measured over a 5-minute period to determine mean ECO in the breath during this period. The control measurements permitted the study ECO breathing air, and the effect of 100% oxygen on ECO, without the influence of extra CO from acute poisoning. Data from the control samples were pooled to establish a normal reference group. The non-smoker and smoker control populations originated from two sources:

(a) Individuals attending a Rockingham-Kwinana District Hospital (RKDH) Health Expo, who attended the "quit smoking" stand at the Expo (included smokers, and non-smokers). This hospital was a district referral hospital of the Fremantle Hospital.

(b) Staff volunteers from the Fremantle Hospital ED, and Hyperbaric Unit.

1 ATA control samples

ECO measurements were obtained from smokers and non-smoking subjects at 1 ATA. All volunteers were provided with an information sheet about the project (see appendix 18.8), and given the opportunity to ask questions. After their consent was obtained (using a parent or guardian if they were a minor), they were connected to the ECO apparatus, and CO readings measured in real-time, first breathing air and then 100% oxygen (figure 7.1). The apparatus depicted in figure 7.1 is available as a kit, with head strap to ensure comfortable placement on the patient. It is the *Hudson Complete IMV System*, Hudson RCI, Temecula, California USA, and at the time of writing (2005) cost $18.32 Australian. It is available to most ED's in Australasia.

Although the strict delivery of 100% oxygen for treatment of CO poisoning is not evidence based, there were other reasons to ensure that 100% oxygen was delivered in my study. Most of the high flow oxygen systems would not allow collection of exhaled gas from the patients because they were open to the environment. This was a practical consideration for my research in collecting exhaled breath samples where I needed a closed system.

It was known from other studies (Weaver et al 2000), that the half-life of COHb elimination varied depending on the P_aO_2, and it was suggested that some of this variability originated from varying F_IO_2 delivered by the non-rebreather face mask. During measurement of ECO elimination, I wanted to remove this potential confounder, so that my elimination half-lives were comparable between individuals receiving the same oxygen concentration. This also allowed a direct comparison of elimination half-lives due to pressure only: breathing 100% oxygen at 2.8 ATA, and 1 ATA, by removing the potential confounding influence of variable F_IO_2 at 1 ATA.

The reservoir bag and oxygen tubing shown in figure 7.1 were removed for air sampling. This allowed air from the environment to be inhaled by the patient via a one-way valve. All exhaled breath was passed through the ECO apparatus via corrugated tubing (figure 6.4). Fresh sterilised masks and tubing were provided for each new subject.

Figure 7.1 100 percent oxygen delivery circuit

When the CO concentration and ventilation were stable, the mean ECO level was recorded each minute over a five-minute period. Results were then tabulated, recording the volunteer's age, sex and documenting their smoking status. If the volunteer was a smoker, additional information was collected. This included: the number of cigarettes smoked each day, the CO content of the cigarette (from the information on the packet) and the time period between the last cigarette and sampling. Smoker controls contributed mean ECO samples measured breathing air, and a smaller subset contributed mean ECO samples breathing oxygen. A subset of non-smokers (n=22) volunteered to have COHb levels measured to correlate these with the ECO readings. Venous blood samples were collected from 41 smokers who volunteered for COHb measurement. Touger et al (1995) found that venous COHb levels were consistently lower in poisoned patients, by a mean of 0.15%, and that there was a strong positive correlation between the arterial and venous COHb levels. Work by Benignus et al (1994) evaluated arterial and venous samples during short-term exposure to CO, and found that lower venous COHb levels occurred during the loading of CO, however steady state was reached after 15 minutes and the values became equal. The potential differences in venous and arterial COHb values were not considered significant enough to affect the relationship between COHb and ECO, and all samples from

volunteers were venous only. Data correlating ECO with COHb from volunteer smokers was amalgamated with acutely poisoned individuals for analysis in chapter 9.

Hyperbaric control samples from divers

Divers referred for treatment of decompression illness were recruited into the study to measure ECO levels breathing air, NBO and HBO. They served as a *hyperbaric* control population. Divers received ethics committee approval for entry as hyperbaric control subjects, because they were accustomed to pressure, and were receiving hyperbaric oxygen treatment at the time of the sampling. This enabled correlation of the effect of pressure on ECO, in the absence of CO poisoning. It was necessary to measure volume for the ECO samples taken from divers in the hyperbaric environment, because although the individuals were treated at 2.8ATA, the breath samples were collected at 1 ATA outside the chamber. Exhaled breath from individuals inside the chamber was continuously channelled through a pipe via a pressure reduction regulator (overboard dump, figure 6.6) to the outside of the chamber. Once outside the chamber the exhaled gas was passed through unidirectional valves to the ECO apparatus sampling port (figure 6.4). A further unidirectional valve on the efferent side of the oxygen analyser prevented backflow of environmental air into the system. Hence it was expected that samples from individuals in the hyperbaric chamber would have RMV's that were increased by a factor of 2.8 in proportion to the hyperbaric treatment pressure. At 1 ATA, divers breathed air and oxygen from the same apparatus as the smoker controls. At 2.8 ATA, the divers breathed 100% oxygen from an aviator style demand valve mask (figure 7.2), which directed all exhaled breath to the ECO apparatus outside the hyperbaric chamber. It was anticipated that this mask may not deliver 100% oxygen at all times due to poor mask fit, and even with appropriate fitting, delivered 96-98% oxygen (Sheffield et al 1975). To overcome this, masks were carefully applied to ensure close fit for each individual, and expired oxygen were monitored during their treatment, in the same way as took place fro individuals treated at 1 ATA.

Figure 7.2 Hyperbaric 100% oxygen delivery system

Previous analysis of the Fremantle Hospital Hyperbaric database showed that there were similar numbers of divers treated for decompression illness (DCI) at identical treatment pressures to those used for individuals with CO poisoning. Divers were expected to be enrolled in similar numbers to those receiving HBOT for CO poisoning during the study period, and could therefore act as contemporary controls. Because divers were fit to be exposed to pressure in the subaquatic environment, and hyperbaric oxygen was the usual treatment for their decompression illness, the potential side effects of hyperbaric oxygen did not create additional ethical issues for this population. Expired CO samples were obtained from the divers at the Fremantle Hospital Hyperbaric Medicine Unit, after obtaining informed consent for their participation in the study, and after providing them with an information sheet.

There was potential for confounding influences if DCI influenced CO excretion. I had been unable to identify any references to this area in the literature, which made it unlikely that DCI would affect ECO. Non-smoking divers were not expected to produce significant quantities of ECO, because their medical screening for fitness to dive (governed by Australian Standards 4005.1 and 2299.1) usually ensured that they were free of chronic respiratory illness. Part of this fitness assessment is directed at excluding respiratory diseases such as asthma, cystic fibrosis and respiratory infections, which have been shown to increase ECO (Zayasu et al 1997, Horvath et al 1998, Yamaya et al 1998, Terheggen-Lagro et al 2003).

Diver smoking status was recorded, then ECO samples obtained breathing air, NBO, and HBO. These were correlated with blood samples measuring COHb. It was expected that there would be low numbers of divers who also smoked cigarettes, because the medical screening process for divers selects against those with respiratory disease, at the time they commence their diving career, and hence selects against smokers. I was reliant on the chance that divers presenting with decompression illness also were smokers.

7.3. Results

The apparatus proved to be portable and easily connected to the exit limb of the breathing apparatus for the control populations breathing air, NBO and for sampling from divers in the HBO environment. During the collection of control data, 213 volunteers with ages ranging from 9 to 75 successfully provided samples. The control population consisted of 80 non-smokers, 119 volunteer smokers, and 14 otherwise healthy divers (all non-smokers). None of the population reported any subjective breathing resistance or mask discomfort when providing samples. Data were normally distributed for the control populations. The demographics of the control populations are summarised in table 7.1

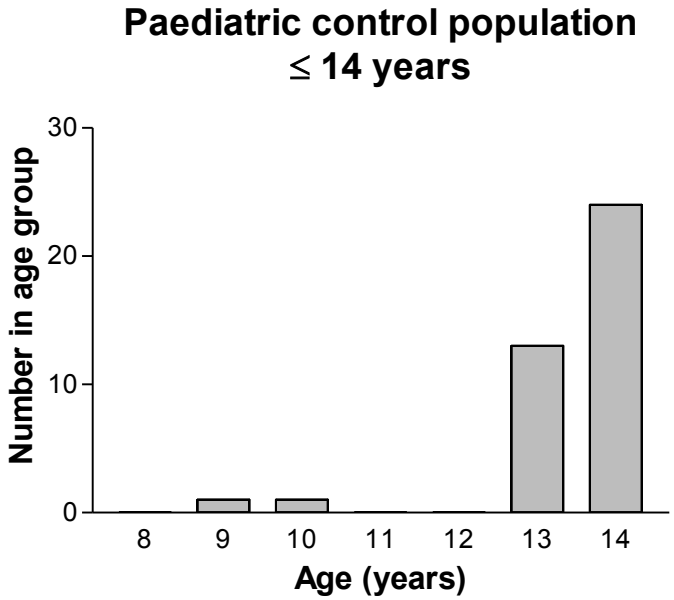
Table 7.1 Demographics of the control populations:

Control Population	**Number**	**Mean Age (95% CI)**	**Standard Deviation Age**	**Number of Females**	**Number of males**
(A) Non-smoker	**80**	32.8 (29.9-36.6)	17.1	44	36
(B) Non-smokers providing air and O_2 samples (subset of A)	31	34.1 (30.1-38.0)	10.8	8	23
(C) Non-smokers providing COHb samples (subset of B)	22	33.8 (28.6-38.9)	11.6	5	17
(D) Smoker Controls	**119**	26.6 (23.8-29.3)	15.1	57	62
(E) Smoker controls providing sample for COHb (subset of D)	41	29.6 (25.6-33.7)	12.9	16	25
(F) Smoker controls with air and O_2 samples (subset of E)	16	32.7 (28.5-36.9)	7.9	7	9
(G) Diver controls (All non-smokers)	**14**	33.7 (29.3-38.2)	7.7	1	13

Paediatric sampling

Using appropriately sized masks, 39 children (aged ≤ 14 years) contributed control samples. Their median age was 14 years, (range 9 to 14), and they reported no perceived breathing difficulty, or mask discomfort. The paediatric population was not normally distributed, as there were a greater number of older children in the smoking population (Figure 7.3).

Figure 7.3 Age distribution of the paediatric control population



7.3.1. Non-smoking control samples.

In the non-smoking controls, ECO breathing air and oxygen, and COHb were extremely low and not normally distributed. Table 7.2 summarises the results for the non-smoking control group. Thirty-one individuals provided matched samples of ECO in air, then NBO. In this group, the ratio of ECO breathing NBO to ECO breathing air was 3.2 to 1. A further 22 provided matched samples of ECO breathing air, and a blood sample for COHb.

Table 7.2 ECO in Non-smokers Breathing Air and Oxygen, and COHb

Non-smoker controls full population (n=80)	**ECO breathing air (ppm)**	
Median	1.0	
25th Percentile	1.0	
75th Percentile	2.0	
Range	0 to 7	
Non-smoker controls matched air and 100% O_2 subset (n=31)	**ECO breathing air (ppm)**	**ECO Breathing 100% O_2 (ppm)**
Median	1	4
25th Percentile	1	3
75th Percentile	1	5
Range	0 to 6	0 to 9
Non-smoker controls matched air and COHb subset (n=22)	**ECO breathing air (ppm)**	**COHb %**
Median	1	0
25th Percentile	1	0
75th Percentile	1	0
Range	0 to 6	0.0 to 1.0

7.3.2. Control samples from smokers breathing air and NBO

A total of 119 individuals provided control samples as smokers (57 females and 62 males). Table 7.3 summarises the data from this population. The data in table 7.3 appears skewed but has been plotted and is sufficiently "normal" to justify the use of means.

For the 41 smokers providing COHb levels, the mean ratio of ECO breathing air (ppm) / COHb (%) was 6.3 ± 4.3 ppm/% (95% CI = 4.7 to 7.7 ppm/%). From this data, for every rise of 1% COHb, there is a corresponding rise of 6.3 ppm ECO breathing air. The subset of 16 smokers who provided both ECO breathing air and ECO breathing 100% oxygen demonstrated mean ECO oxygen to air ratio of 4.1 ± 1.0 (95% CI = 3.5 to 4.7).

Table 7.3 ECO in Smokers Breathing Air and Oxygen, and COHb

(a) Smoker controls full population (n=119)	**ECO breathing air (ppm)**	**Age**	**Number of Cigarettes Smoked per day**	**Time since last Cigarette (minutes)**	**Cigarette CO Content (mg)**
Mean (SD)	15.9 (10.2)	26.6 (15.1)	15.7 (10.1)	94.7 (181.0)	12.0 (4.3)
95% CI	14.1 to 17.8	23.8 to 29.3	13.9 to 17.6	61.9 to 127.6	11.2 to 12.9
Range	1 to 40	9 to 75	1 to 40	1 to 900	2 to 18
(b) Smoker controls matched air and COHb subset (n=41)	**ECO breathing air (ppm)**	**COHb (%)**	**Number of Cigarettes Smoked per day**	**Time since last Cigarette (minutes)**	**Ratio ECO breathing air (ppm) to COHb (%)**
Mean (SD)	14.5 (11.6)	2.5 (1.9)	15.2 (9.7)	167.9 (246.2)	6.3 (4.3)
95% CI	10.9 to 18.2	1.9 to 3.1	12.2 to 18.3	90.2 to 245.6	4.7 to 7.8
Range	1 to 40	0 to 7	1 to 40	1 to 900	1.1 to 18.7
(c) Smoker controls matched air, 100% O_2 subset (n=16)	**ECO breathing air (ppm)**	**ECO Breathing 100% O_2 (ppm)**	**Number of Cigarettes Smoked per day**	**Time since last Cigarette (minutes)**	**Ratio ECO (ppm) breathing O_2 to ECO (ppm) breathing air**
Mean (SD)	7.4 (4.1)	28.3 (14.5)	16.4 (8.3)	163.4 (232.3)	4.1 (1.0)
95% CI	5.2 to 9.6	20.5 to 36.0	12.0 to 20.8	39.7 to 287.2	3.5 to 4.7
Range	1 to 19	6 to 69	5 to 30	5 to 900	2.3 to 6.0

To further assess ECO measurements taken using the ECO apparatus, an attempt was made to correlate ECO measurements with the time since last cigarette, number of cigarettes smoked per day, and the CO content of the cigarette. There was a strong negative correlation between the elapsed time since the last cigarette, and the level of ECO in the breath ($r^2 = 0.22$, and $p<0.0001$). The results are depicted in figure 7.4. However, when the linear regression line was compared with a single- phase exponential decay curve, the latter produced a better fit. The decay half-life for the population was 68.1 minutes (95%CI= 40.1 to 224.6 minutes), figure 7.5.

Figure 7.4 Graph Showing Time since Last Cigarette vs ECO Breathing Air using linear regression

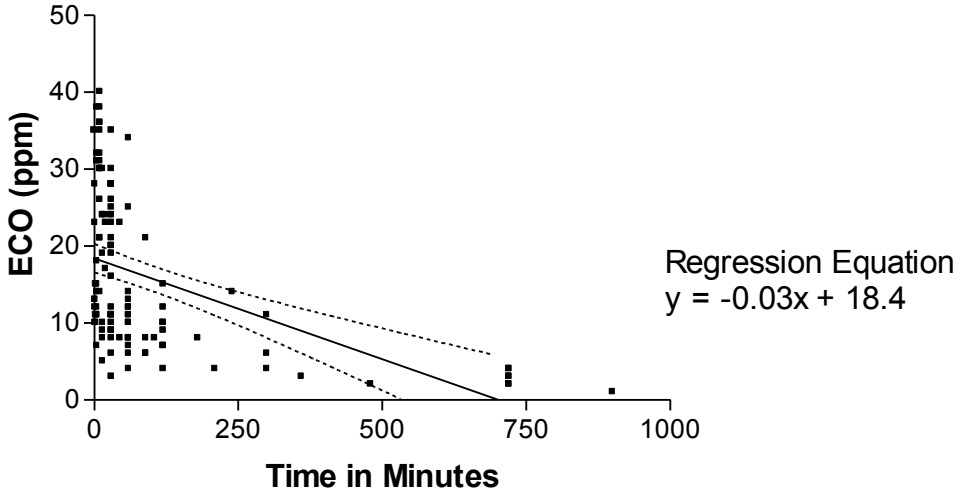
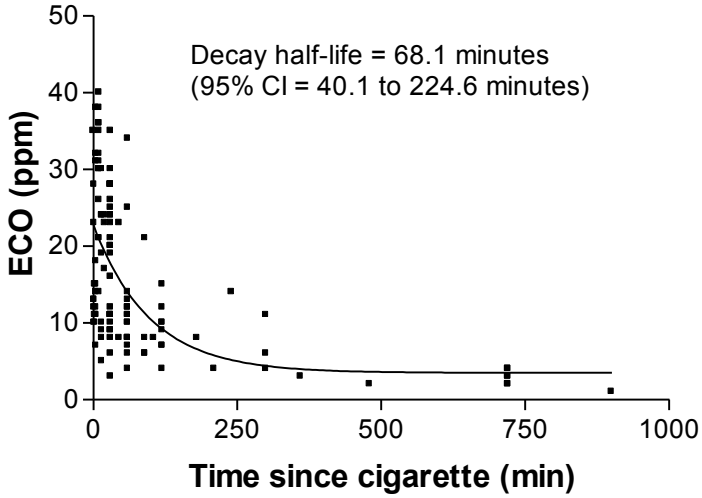
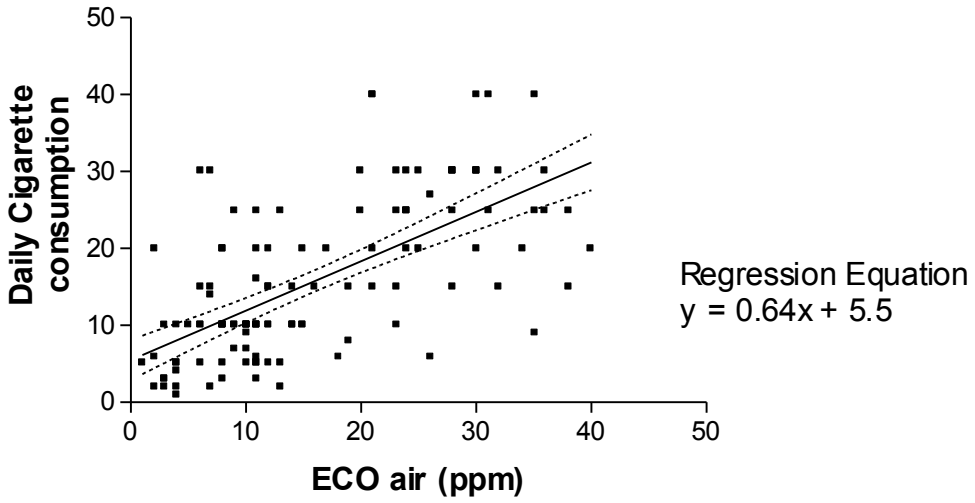


Figure 7.5 Graph Showing ECO vs Time since Last Cigarette Breathing Air



There was a strong positive correlation between the daily number of cigarettes smoked and the amount of CO excreted in the breath (r^2= 0.42, p<0.0001). The results are shown in figure 7.6:

Figure 7.6 Graph Showing Cigarettes Smoked per Day vs ECO Breathing Air



The relationship between CO content of the cigarettes and ECO breathing air was not statistically significant. (r^2=0.02, p=0.16).

7.3.3. Control samples from divers with decompression illness.

This group consisted of 13 males and one female. All were non-smokers. Table 7.4 outlines the ECO values for non-smoking divers from this data. The data in table 7.4 appears skewed but has been plotted and is sufficiently "normal" to justify the use of means.

Table 7.4 ECO and CO Offgassing for the Diver Controls

	ECO Breathing Air (ppm)	**CO Offgassing Breathing Air mL/Min**	**ECO Breathing 1 ATA O_2 (ppm)**	**CO Offgassing Breathing 1 ATA O_2 mL/min**	**ECO Breathing 2.8 ATA HBO (ppm)**	**CO Offgassing Breathing 2.8 ATA HBO mL/min**	**COHb (%)%**
Mean (SD)	1.1 (0.9)	0.012 (0.009)	3.9 (1.7)	0.05 (0.03)	4.6 (2.1)	0.13	0.03 (0.07)
95% CI	0.5 to 1.6	0.006 to 0.017	3.0 to 4.9	0.029 to 0.067	3.4 to 5.8	0.09 to 0.17	0.0 to 0.07
Range	0 to 4		2 to 9		3 to 11		0.0 to 0.2
ECO Ratios		**O_2/Air**		**HBO/Air**		**HBO/O_2**	
		3.6		4.2		1.2	
Offgas Ratios		**O_2/Air**		**HBO/Air**		**HBO/O_2**	
		3.91		11.11		2.85	

From the table it can be seen that adding 100% oxygen increases the amount of ECO by a factor of 3.6. When CO offgassing is calculated allowing for RMV, this ratio is 3.9. The addition of Hyperbaric 100% oxygen at 2.8 ATA did not significantly change the concentration of ECO when compared with 100% oxygen ($p=0.38$, table 7.4). However, when CO offgassing was measured, taking into account RMV, hyperbaric oxygen at 2.8 ATA produced a proportionate increase in CO offgassing by a factor of 2.85. After the exhaled breath from hyperbaric samples had expanded to 1 ATA, there was a measured significant increase in RMV in proportion to the pressure (mean of differences = 16.9 L/min, $p < 0.0001$). The difference in CO offgassing between NBO and HBO could be entirely accounted for by the elevation in ambient pressure in the absence of significant changes in the ECO concentration.

When the population of non-smoker diver controls were compared with the other non-smoker controls, there a trend towards lower ECO values in the divers, but the difference was not statistically significant ($p=0.08$). When breathing 100% oxygen, the two control populations did not have

significantly different ECO values (p=0.83). This indicated that the non-smoker and diver controls could not be distinguished from each other measuring ECO. Repeated measures analysis of variance for the matched samples of divers exhaling CO in air, 100% oxygen and HBO produced a highly significant result, $p < 0.0001$, indicating that as the $P_IO_2$was increased, so did the excretion of CO.

7.4. Discussion

When breathing air, low levels of ECO were detected in the population of healthy non-smokers, and non-smoker divers (tables 7.2 and 7.4). Low levels were expected, because the individuals had not been exposed to exogenous sources of CO, such as tobacco smoke, or exhaust fumes. The likely sources of CO in this population were endogenous production, or small amounts of CO inhaled from the environment. None of the volunteer subjects were exposed to polluted environments on the day of sampling. My results are consistent with those of Yamaya's group (1998) who detected 1.2 ± 0.3 ppm CO in the exhaled breath of healthy controls. Similar readings of 1.7 ± 0.1 ppm were obtained for healthy non-smoker controls by Zayasu et al (1997). It was noted by Yamaya et al and Zayasu et al in each of the above studies, an increase in baseline CO offgassing resulted from upper respiratory tract infections and asthma. This was presumably due to activation of airway haem-oxygenase with airway inflammation. I did not investigate the effect of respiratory disease in this study however, control subjects were free of respiratory symptoms.

Smoker ECO readings were significantly higher than those in non-smokers (table 7.3). Smoker ECO measurements were also higher than the 5.8ppm ECO observed by Horvath et al (1998) in non-smokers with asthma. This was expected, given that cigarettes are a known source of CO. My findings were consistent with Zayasu et al (1997) who found that smokers had CO breath readings of 21.6 ± 2.8 ppm when breathing air. It is not possible to compare in detail, my data with Zayasu's group, as precise details of the smoking habit of their population was not described – Zayasu et al's subjects may have had higher cigarette consumption, or less delay between smoking and sampling.

The subset of smokers breathing air who also had COHb levels taken demonstrated a mean ECO/COHb ratio of 6.3 ppm/% COHb. This value is within the range of 5.0 to 1quoted in the Bedfont Smokerlyser manual (Bedfont Scientific Limited, undated).

Increasing the F_IO_2 resulted in higher measured ECO in the smokers. The ratio of ECO breathing oxygen versus ECO breathing air was 4.1±1.0. The expected ratio in proportion to the F_IO_2 breathing oxygen compared with air would be 100/20.9 = 4.8.

All subjects who provided ECO samples when breathing 100% oxygen were staff from Fremantle Hospital, introducing possible selection bias. Staff were not allowed to smoke whilst working. Hence, these subjects had longer delays since their last cigarette compared to the larger population of smokers

but they had similar cigarette smoking patterns. The time delay between smoking and the ECO sampling is one possible explanation for their lower mean ECO.

There was a strong positive correlation between the number of cigarettes smoked per day and the amount of CO detected in the breath. As expected there was a strong negative correlation noted for the level of ECO versus the time since last cigarette, due to offgassing of CO. This was expected, because the lungs are known to be the main excretion endpoint for carbon monoxide that is loaded into the body during smoking of the cigarette. Elimination of CO for the smokers followed a single-phase exponential pattern. This has been noted in studies by other authors (Pace et al 1950, Peterson and Stewart 1970, Wagner et al 1975, Weaver et al 1994, Levasseur et al 1996, and Jay and McKindley 1997). It will be investigated further in Chapter 13. There was a considerable variation in times since last cigarette, among the volunteer subjects, which was a product of the convenience sampling method used. This may have affected the validity of the results, particularly when trying to correlate ECO with CO content in the cigarette. Unfortunately a series of time-matched samples was not undertaken.

Delays to sampling may have caused Fremantle Staff controls to have lower ECO levels when providing 100% oxygen samples. It was not possible to demonstrate a clear relationship between the CO content of the cigarette, and CO offgassing. This may have been due to greater influence from the other factors, such as the time delays to sampling.

Mean ECO in non-smoking healthy divers breathing air was similar to other non-smokers, and similar to results published previously (Zayasu et al 1997, Yamaya et al 1998).
Breathing 100% oxygen, divers had their measured ECO increased by a factor of 3.9 compared with air. Breathing 100% oxygen at 2.8 ATA, there was an insignificant increase in ECO concentration, compared with 100% oxygen at 1 ATA. Compared with breathing 100% oxygen at 1 ATA, carbon monoxide offgassing increased by a factor of 2.85 when breathing HBO at 2.8 ATA. This was almost directly proportional to the increase in pressure. From this data, it appears that the effect of enhanced CO excretion from the HBO environment is mostly due to the increased pressure, causing an increase in gas density and partial pressure in the lung. When this gas was depressurised to the 1 ATA environment, it expanded in proportion to the pressure reduction, causing increased volume of CO excreted. Repeated measures analysis of variance for the matched samples of diver CO offgassing demonstrated that excretion of CO increased as the P_IO_2 was increased. This was previously known to

occur for removal of CO from haemoglobin, however this study provides the first demonstration of the effect using breath measurements

7.5. Conclusions

Baseline levels of ECO are low in healthy non-smoking volunteers. Divers treated for decompression illness were all non-smokers and had low levels of CO in their ECO samples. Smokers have higher baseline ECO than non-smokers. Smoker ECO levels correlated positively with the number of cigarettes smoked per day, and negatively with the time since last cigarette. Carbon monoxide elimination from smokers was consistent with a single-phase exponential process. It was not possible to demonstrate a significant correlation between the cigarette CO content and the ECO.

Expired CO increased as a function of increased P_IO_2 for smokers and diver controls. This is the first time that this phenomenon has been documented measuring ECO.

Under hyperbaric conditions at 2.8 ATA, CO offgassing in divers increased by a factor of 2.85, however there was no significant increase in mean ECO concentration breathing HBO. The increased CO offgassing most likely resulted from increased gas density in the hyperbaric environment, which resulted in greater volumes excreted, when the exhaled gas was depressurised and measured outside the hyperbaric chamber at 1 ATA.

8. A CLINICAL CASE SERIES OF POISONED PATIENTS

Introduction

This chapter provides an overview of the recruitment, demographics, poisoning source, neurological status at presentation, and the treatment of the prospective case series of CO poisoned patient presented in chapters 9 to 15. Data collected from the patients was used in a number of different analyses in the chapters that follow. The methods describe how the prospective case series was derived, and which patients were used in each of the chapters 9 to 15.

8.1. Aims

The aims of this chapter were:

(1) To enrol consecutively a prospective case series of CO poisoned individuals, for the purpose of studying ECO as a marker of CO poisoning.

(2) To examine the demographic features of the poisoned individuals, including their age, sex, smoking status, whether the poisoning was accidental or deliberate, the source of the CO, whether or not individuals had LOC, and their neurological status at presentation.

(3) To summarise how the case series was studied in the following chapters 9 – 15.

8.2. Methods

8.2.1. Selection of cases and projected numbers

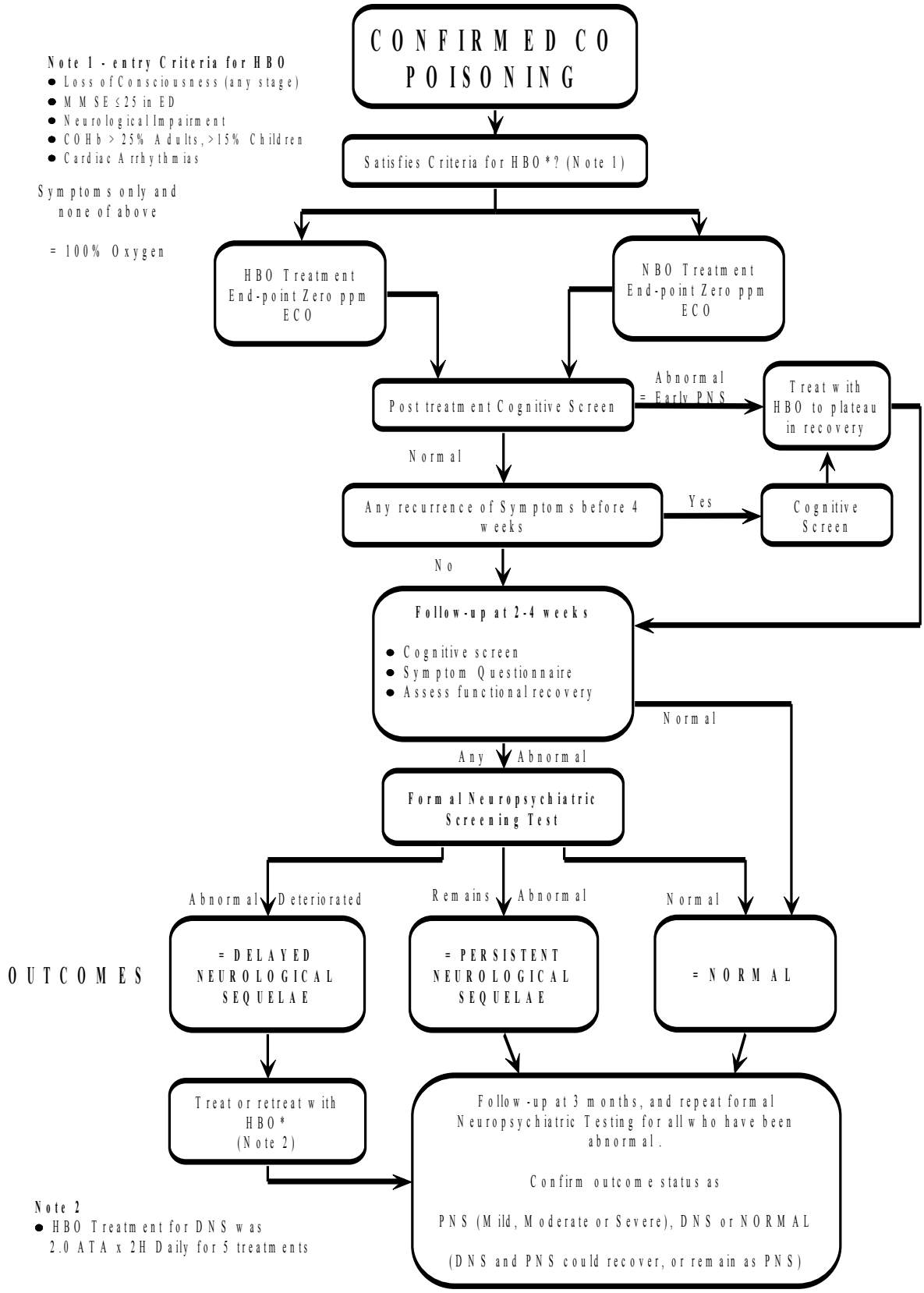
This prospective case series consecutively enrolled patients referred to receive treatment for acute CO poisoning at Fremantle Hospital from April 1992 to September 1993.

Fremantle Hospital was the Western Australian State referral centre for Hyperbaric Medicine and the only civilian hyperbaric chamber in metropolitan Perth (Population 1.2 million people). In the years 1990 and 1991 there had been approximately 30 individuals treated for CO poisoning each year at the Fremantle Hospital Hyperbaric Medicine Unit. Therefore we expected to enrol by convenience, 40 – 50 patients over a period of 18 months. Sample size was not calculated, because this was not a randomized, controlled trial that compared two treatments, with an expected difference in outcomes. It was planned to undertake a number of analyses on the CO poisoned patients entered into the study, as outlined in the thesis aims (chapter 4):

8.2.2. Study design

Patients were consecutively enrolled, then allocated to treatment groups using a protocol that assessed their clinical status at entry. More severely poisoned patients were allocated to the 2.8 ATA Hyperbaric Oxygen (HBO) treatment arm, and less severely poisoned patients received 100% oxygen at 1.0 ATA (NBO) (Table 8.1). Measures of outcome were mortality and the numbers of patients who had PNS or DNS as defined in the literature review, at three months follow-up. Figure 8.1 summarises the entry criteria and study protocol.

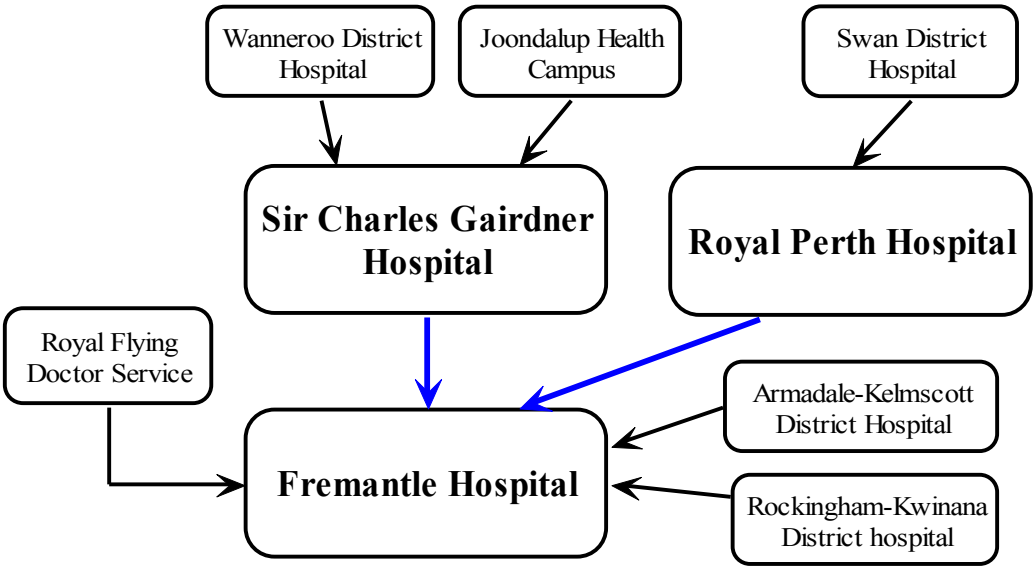
Figure 8.1 Flowchart summarising the process of enrolment, assessment and treatment of CO poisoned patients.



8.2.3. Research setting

The research was undertaken in at Fremantle Hospital in Perth, Western Australia, a city of 1.2 million people. Fremantle Hospital was one of three major teaching hospitals, all affiliated with the University of Western Australia. Fremantle Hospital had Western Australia's only civilian hyperbaric facility, and was the state's tertiary referral centre for diving and hyperbaric emergencies. Each of the teaching hospitals had peripheral district hospitals, from which they received referrals. Fremantle Hospital was closely linked with Rockingham-Kwinana District Hospital (40 km south), and Armadale-Kelmscott District Hospital (30km east). Some staff were shared, and Fremantle Hospital adopting a "parent-sibling" relationship with these two hospitals. This relationship also facilitated research, in that the three hospitals effectively constituted "one campus". The relationships of all of the Perth Metropolitan Hospitals, and the Royal Flying Doctor Service (for intrastate Hyperbaric Emergency transfers), are shown in figure 8.2 below (tertiary hospitals are shown in bold):

Figure 8.2 Relationships of Perth hospitals



8.2.4. Research ethics approval and consent

Approval was granted for the project by the Research and Ethics Committee of Fremantle Hospital (a teaching Hospital of the University of Western Australia) in March 1992. The research application and approval constitutes appendix 18.8. The project was undertaken from April 1992 to September 1993, with final outcome analysis for the last cases completed in January 1994. In all circumstances where data was collected from volunteers or patients, written informed consent was obtained. If patients were incapable of informed consent due to their clinical condition, or were minors, next of kin or a primary relative provided the written informed consent. Patients who did not wish to participate in the clinical trial received the standard treatment determined by pre-existing guidelines at Fremantle Hospital.

8.2.5. Notification of ED's and prehospital care

All ED Directors in the Perth (WA) metropolitan area received written notification of the trial, to facilitate referrals in accordance with the study protocol. I conducted a number of education presentations to metropolitan ED's, including instruction on the entry criteria, and initial data collection, using preformatted forms. Contact numbers were provided to facilitate referral of poisoned patients in accordance with the study protocol. St John Ambulance (WA) was notified of the trial. Normal prehospital treatment protocols were followed to minimise the effect on the St John Ambulance Service. Prehospital treatment consisted of high flow oxygen by soft plastic face mask with reservoir if the patient was spontaneously ventilating, or high flow oxygen via Laerdal® bag and mask (1.6 L bag volume with 2.6 L reservoir) if ventilatory assistance was required. Treatment for CO poisoned patients in the ED's incorporated of 100% oxygen therapy. The method for this had been widely circulated to the Perth Metropolitan Hospital ED's in the form of a detailed review article on oxygen therapy, and equipment demonstration (Smart and Mark 1991 [1 and 2]).

Initial neurological and cognitive assessment was carried out in the ED of either Fremantle Hospital or the referring hospital. Patients were then assessed to determine if they had criteria for entry into the trial. These criteria are summarized in table 8.1 below. Patients with criteria requiring HBO treatment were referred to the Fremantle Hospital for treatment. Transfer then occurred by road ambulance using St John Ambulance (WA), as per existing procedures.

Table 8.1 General entry criteria for the prospective study

All Patients Significant exposure to carbon monoxide that caused symptoms or physical impairment
HBO Treatment - Entry criteria - one or more of • Loss of Consciousness at any stage of the CO exposure • Ongoing neurological abnormality or impairment of consciousness • Cognitive impairment in the ED (MMSE score of ≤ 25/30) • Cardiac Arrhythmias • COHb ≥ 25% for Adults, and COHb ≥ 15% for children
NBO Treatment • Confirmed exposure to CO with ongoing symptoms • No loss of consciousness • No neurological/cognitive abnormality, • COHb levels less than indication for HBO

The HBO treatment arm was derived from all patients from Perth Hospitals who had clinical CO poisoning of sufficient severity as defined by the entry criteria in table 8.1. Individuals with less severe CO poisoning satisfying criteria for NBO were treated at their local hospital and were not entered into the study, due to the substantial geographic separation of the metropolitan hospitals in Perth (up to 100 km apart). The NBO study group therefore constituted referrals from Fremantle Hospital only. A selection bias was expected as a result of this protocol, with unequal numbers in the two treatment arms. The impact of this will be covered in the chapters to follow.

8.2.6. Initial assessment at Fremantle Hospital ED

When CO poisoned patients arrived at Fremantle Hospital, the normal emergency treatment regimen was followed. Life support measures were instituted and continued. Patients were clinically assessed at presentation by full history and examination. An intravenous cannula was inserted and blood taken for COHb level. Blood gas analysis was performed to assess for acidosis. Their Glasgow coma score was recorded (GCS, appendix 18.2.1). The mini-mental state examination (MMSE, appendix 18.2.2) was used as the screening tool for cognitive deficits, where the patient's clinical status permitted. This had been previously validated as a screening test for detection of cognitive disorders (Folstein et al 1975, Tombaugh and McIntyre 1992). A neurological rank was assigned to the patients at entry, using the criteria in table 8.2.

Table 8.2 Patient neurological ranks in the ED

Ranking	Definition	Clinical Description
1	Coma	GCS ≤ 8
2	Neurologically impaired	GCS=9-13
3	Cognition Impaired	GCS ≥ 14 and MMSE ≤ 25
4	Normal	GCS=15 and MMSE≥26.

Patients were allocated to treatment groups according to the criteria in table 8.1.

8.2.7. NBO treatment

All poisoned individuals were treated with oxygen as soon as possible after rescue. Spontaneously ventilating patients transported by ambulance received high flow oxygen by soft plastic face-mask, or intermittent positive pressure ventilation was delivered using a Laerdal® bag if ventilatory assistance was required.

When patients arrived in the ED, they were treated with oxygen, by the following methods:

(1) If they required ventilatory assistance, or were significantly obtunded - endotracheal intubation and 100% oxygen

(2) If spontaneously ventilating, and cooperative - 100% oxygen was delivered by either a Laerdal® circuit, or a soft face mask attached to the patient's head and a 3 Litre reservoir bag, with a one-way non-rebreathing circuit directing the oxygen using low resistance valves (see figure 7.1). Oxygen flow rate was adjusted to suit the respiratory demands of the patient (up to 30 LPM). One hundred percent oxygen was delivered according to the methods described by Smart and Mark in 1992. If patients were uncooperative on application of oxygen, they were nursed on a 1:1 basis, assisted by the author, until they became cooperative.

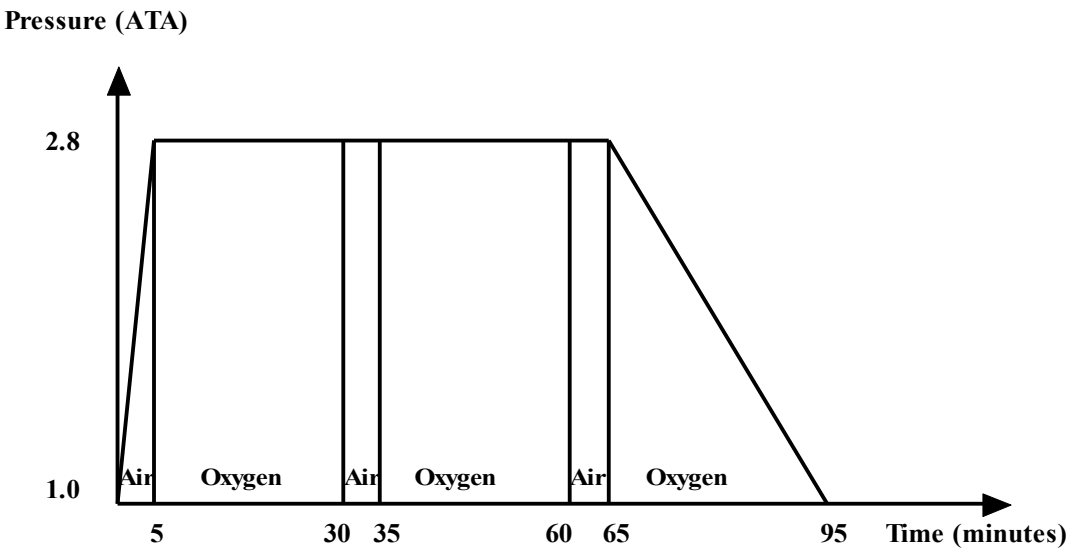
8.2.8. HBO treatment

Fremantle ED patients and patients from other hospitals who were allocated to HBO treatment, were transferred to the hyperbaric facility, continuing the oxygen treatment commenced by the referring hospital. On arrival at the hyperbaric chamber, usually there was a brief period (5-10 minutes) of breathing air as patients were moved into the hyperbaric chamber before pressurisation. During this time the patient's condition was monitored, and if there was any deterioration, or a fall in oxygen saturation to less than 90%, then supplemental oxygen was restored. Ventilated patients received 100% oxygen during both transfer into the chamber and during pressurisation.

The planned HBO treatment consisted of pressurization breathing air to 2.8 ATA over approximately 5 minutes, followed by 60 minutes at treatment pressure (two cycles of 25 minutes oxygen, 5 minutes air), then 100% oxygen breathed over 30 minutes while the chamber was depressurized (FH-18, or 18:60:30 table - see figure 8.4).

Hyperbaric Oxygen treatment was delivered in a triple lock multiplace facility, with main chamber capability 3.0 atmospheres pressure, and the smaller "diving chamber" capability 6.0 atmospheres pressure (see figure 8.5). Spontaneously ventilating patients were placed supine, or semi recumbent, and oxygen delivered via an "aviator style" demand-valve built in breathing set (BIBS) face-mask (figure 7.2). If patients could not equalise during pressurization, attempts were made using alternative measures such as swallowing water, or swallowing with the nose blocked (the Toynbee manoeuvre), and with the use of decongestants. In extreme circumstances, a myringotomy was required.

Figure 8.4 FH-18, or 18:60:30 HBO treatment table



The first 2.8 ATA HBO treatment was provided as soon as possible after poisoning, followed by a second identical treatment at 2.8 ATA within 6 - 12 hours. If the patient continued to detectable ECO, then subsequent HBO treatments were administered at 8 - 24 hour intervals until ECO was undetectable in the breath when sampling from hyperbaric conditions. Patients did not receive supplemental oxygen between HBO treatments, unless clinically indicated for hypoxia.

Figure 8.5 Hyperbaric oxygen treatment facility, Fremantle Hospital

8.2.9. ECO measurement and data collection

The exhaled CO concentration was recorded every five minutes during HBO treatments, and every 10 minutes during NBO treatment. When ECO fell to zero (the expected treatment end-point), neurological and cognitive status was assessed by the treating physician.

If patients had returned to normal, then they were discharged from the hyperbaric medicine unit for ongoing care at their referring unit, including psychiatric assessment if appropriate. Patients and their relatives were given a printed handout outlining the type of symptoms which may occur between treatment and contact details of the investigators, if they or their relatives noted problems.

Patients who had not returned to normal neurological/cognitive status when ECO was undetectable were given a more extended regimen of HBO treatment, as described below. If they did not respond to the extended regimen of treatment, they were then referred for rehabilitation by their treating medical team. All patients were followed up and assessed at two to four weeks, and again at three months. Any patients with DNS from either treatment group received further HBO treatment (5 x daily treatments at 2.0 ATA for 2 hours).

Because ECO had not been used before to monitor treatment, and zero ECO had not been tested as a treatment end-point, it was necessary to provide a "safety net" treatment option in the event of patients failing to return to normal neurological and cognitive function when ECO was unrecordable. Patients were treated with an extended HBO regimen until their neurological and cognitive function normalised or plateaued over three consecutive treatments. This was a requirement of the research proposal to the ethics committee, because it reflected existing practice prior to the study. Clinical assessment of the patient occurred between hyperbaric treatments, or at the end of 100% oxygen treatment and the decision to enter the extended HBO regimen was based on abnormalities detected at these examinations. (See figure 8.1).

Patient neurological and cognitive status at treatment end-point was compared to their final status at 3 months, to determine if early abnormalities were predictive of PNS. Patients who had PNS were

classified as “poor” outcomes, because zero offgassing did not predict acute recovery from their CO poisoning (see below for more detailed description of cognitive assessment).

Demographic, treatment and outcome data were entered into a Microsoft® Access database, and CO offgassing data were stored in Microsoft® Excel 5.0 spreadsheets (Microsoft Corporation, Roselle Illinois USA). Data collection sheets are included in the appendices. Demographic data included patient’s age, sex, smoking status, reason for their CO exposure (suicidal or accidental), duration of exposure, source of CO, time from rescue to study entry, to 100% oxygen, and to hyperbaric oxygen (if administered). Also recorded were: whether or not they had lost consciousness, neurological state at arrival at the hospital including their conscious state, main symptoms at presentation and consumption of other drugs if they had been suicidal. Initial MMSE scores, COHb levels, lactate levels, and pH were recorded.

Baseline ECO measurements on air, during their NBO and HBO treatments were recorded in the database. The CO offgassing during patients’ treatment was recorded in the database. Cognitive function test results and neurological ranks were recorded after treatment, and also patient outcomes (normal, DNS, PNS, or death). The database also recorded the results of the functional status questionnaire (FSQ appendix 18.3), and the general health questionnaire (GHQ-12, appendix 18.4). The FSQ was developed to detect symptoms that could be due to sequelae of CO poisoning, and the GHQ-12 has been previously validated to measure minor degrees of psychological distress (Goldberg and Blackwell 1970, Pevalin 2000).

8.2.10. Cognitive testing

The mini-mental state examination (MMSE, appendix 18.2.2) was universally used in Perth Metropolitan Hospital ED’s as a screening test of cognitive function, and allowed pre-treatment cognitive data to be collected. An advantage was that the MMSE could be quickly administered by non-psychologists, allowing rapid assessment of patient’s cognitive function before treatment. Detection of cognitive impairment in this test was used as one of the indications for referral for HBO treatment. Post treatment and follow-up cognitive function testing at 3 months, by neuropsychologists is described in more detail in chapter 14, and appendices 18.2.3 and 18.2.4.

8.2.11. Stratification of patients according to entry delay

Patients were stratified according to the delays from rescue to study entry, based on the work of other authors (Goulon et al 1986, Raphael et al 1989, Thom et al 1995, Mathieu et al 1998, Weaver et al 2002). The stratification was: ≤6 hours, >6 but ≤12 hours, and >12 hours since poisoning for outcome analysis. This stratification also assisted the process of defining study subgroups (described below).

Patient data used in Chapters 9 – 11

Data from patients who were acutely poisoned less than or equal to 6 hours previously were used in chapters 9, 10, and 11 of the research to investigate:

- The relationship between ECO and COHb in poisoned patients
- The effect on ECO of increasing the partial pressure of oxygen in breathing air, of 100% oxygen and of HBO.
- The use of ECO to diagnose CO poisoning, differentiating poisoned individuals from smokers and non-smokers.

Patient data used in chapter 12

In chapter 13 the factors affecting CO load for all patients in the clinical series were investigated.

Patient data used in chapter 13

A sample of CO poisoned patients with initial ECO > 10 ppm was selected to investigate the elimination kinetics of ECO (CO offgassing).

Patient data used in chapters 14

In chapter 14, the usefulness of unrecordable ECO as a treatment endpoint for all patients in the clinical series was investigated.

Patient data used in chapter 15

Chapter 15 assessed the factors at study entry that were associated with good and poor outcomes. All patient data were used except for refusals, exclusions and those lost to follow-up.

8.2.12. Statistical methods

Statistical analysis of data was undertaken using Graphpad® Prism version 2.0 software. Data were presented as mean and SD, median and interquartile range, or number and percent. Continuous data were initially assessed for fit with a normal distribution, then analysed by paired and unpaired Student's t test, or Wilcoxon rank sign test, or Mann-Whitney U test as appropriate. Receiver operator characteristic curves were calculated where appropriate. A curve-fitting program for assessment of "best fit" equations using sum of least squares method was used for analysis of ECO elimination kinetics. Half-lives were calculated from the curves, where data were consistent with first order exponential decay. Analysis of Variance (ANOVA) was used where appropriate. A p value of 0.05 was chosen as the type 1 error for all studies. Proportions were compared using the χ^2 test (with Yates correction), or Fisher's exact test. Odds ratios and 95% confidence intervals were used for proportions, and differences between means.

8.2.13. Ethical considerations

Patients received standard treatment regimens in this study. All patients were able to receive HBO treatment if 100% oxygen failed, or extended periods of treatment if zero ECO proved to be an ineffective marker of treatment endpoint.

Other ethical issues related to the collection of blood samples for COHb.

1. Two extra samples of venous blood were collected from the CO poisoned patients, in addition to those required for routine management. Firstly, at the end of the initial HBO treatment and secondly, at the start of subsequent HBO treatments.

2. Two additional samples of venous blood were collected from divers treated in the chamber.

3. Single venous blood samples were collected from volunteer controls.

Written consent was obtained from the patients or their next of kin at entry to the study, before any of the study blood samples were taken. As all CO poisoned patients and many divers already had intravenous cannulae in situ, blood samples were taken from this cannula to minimise discomfort.

Sampling of expired breath from the patients was completely non-invasive. As described in chapter 7, individuals from the control population reported no discomfort or difficulties with breathing

resistance, and it was expected that sampling from the breathing apparatus would be safe and without interference to their treatment.

8.3. Results

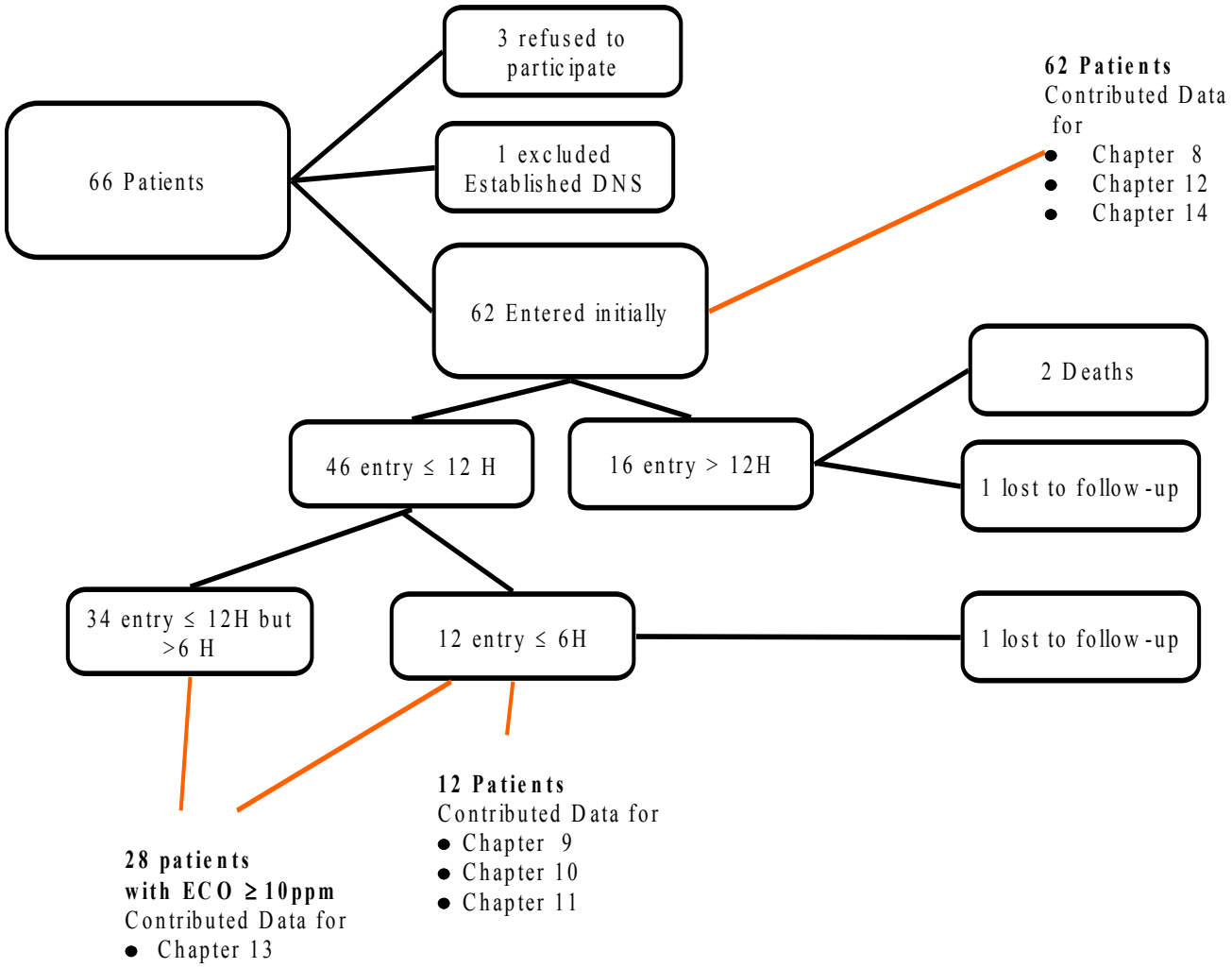
Sixty-six patients were eligible for entry to the study. Three patients refused to participate. An additional patient was referred at 3 weeks after CO poisoning with an established DNS**.** This patient was outside the study protocol and although he gave permission and signed consent for his data to be used in the study, he was excluded from outcome analysis. His clinical record is included in appendix 18.7. Sixty-two individuals were studied in chapters 8, 12 and 14. Of the 62 patients enrolled in the study, two did not receive formal follow-up. They are described later in this chapter (both were treated with hyperbaric oxygen). Sixty patients received full follow-up (96.8%). Forty-seven were allocated to receive hyperbaric oxygen and thirteen received one hundred percent oxygen at ambient pressure. All patients in the study required some intervention to correct a leaking mask, to ensure 100% oxygen was continuously delivered. The frequency of these interventions was not recorded. This supported my decision to measure oxygen concentration in this study

Forty-six patients were entered into the study ≤ 12 hours after their poisoning, and 16 were entered > 12 hours. Of the 46 individuals entered < 12 hours after poisoning, 25 contributed data for the study of CO elimination kinetics in chapter 13. Of the 46, 12 were entered at < 6 hours. This group of acutely poisoned individuals contributed data for chapters 9, 10 and 11. In chapter 10, the acutely poisoned patients also had ECO samples while receiving HBO environment. This permitted correlation of ECO and COHb in air, NBO and HBO. In chapter 11, the 12 acutely poisoned patients were compared with control smokers and non-smokers to assess ECO as a diagnostic tool for CO poisoning.

Figure 8.6 summarises the clinical series of patients and how they were allocated for analysis in chapters 9 - 14.

Figure 8.6

Summary of clinical series of patients and their analysis in the chapters of this thesis



8.3.1. Description of the study population

Appendix 18.1 details the characteristics of the study population at the time of entry. A total of 66 patients (52 males and 14 females) were eligible for entry into the study. Table 8.3 summarises the demographics of the population.

Table 8.3 Demographics of study population

	Males	Females	Comparison males vs females
Number	48	14	
Age (Mean ± SD)	28.5 ± 1.8 (range 3 - 59)	20.6 ± 3.2 (range 6 - 42)	p = 0.03
Smokers	21	2	p = 0.01
Deliberate Self-Harm	37	4	p = 0.001
Accidental Domestic environment	10	10	NS
Accidental Industrial Environment	2	0	NS
LOC	31	8	NS

For the 62 cases entered in the study, the sources of CO were cars in 45 cases (leaded petrol 29, unleaded petrol 14, unknown 2), and barbecues operated indoors (15 cases). The remainder were due to exposure to an indoor fork-lift truck using liquid propane gas (LPG) and diesel motor exhaust. The excluded case CO source was a faulty LPG refrigerator inside a caravan.

8.3.2. Neurological rank in the ED

Table 8.4 shows the duration of loss of consciousness (where known) for patients in this series classified by their clinical neurological grade.

Table 8.4 Relationships between duration of loss of consciousness, delay to treatment, and ED neurological rank

Duration of LOC (Minutes)		ED neurological rank			
		Normal 4 n = 22	**Cognition Impaired 3** n = 27	**Consciousness Impaired 2** n = 7	**Coma 1** n = 6
	Mean (median)	40.8	39.8	272.9	203.3
	SD	113.5	66.7	309.6	111.3
	Lower 95% CI	0.0	11.6	0.0	86.5
	Upper 95% CI	91.1	67.9	559.1	320.1
	Comment	16 patients had no LOC	6 patients had no LOC		

Patients from clinical neurological ranks 1 and 2 were combined then compared with combined ranks 3 and 4. There was a statistically significant difference in duration of loss of consciousness for patients who presented as ED clinical neurological ranks 1 and 2 (neurologically impaired or coma), compared with those who presented as ED clinical neurological ranks 3 and 4 (cognition impaired or normal). The group with the more severe clinical poisoning had longer duration of loss of consciousness (mean LOC = 240.8 minutes compared to 40.2 minutes, difference between means = 200.5 minutes, 95% CI = 116.1 to 284.9 minutes, $p < 0.0001$).

The relationship between time delay to treatment and ED clinical neurological rank was not statistically significant, when grades 3 and 4 were compared to grades 1 and 2. Mean delay for grades 3 and 4 = 248.5 minutes, compared to grades 1 and 2 = 516.3 minutes, difference between the means = - 267.8 minutes, 95 % CI = -76.2. to 611.9, ($p = 0.12$). The regression slope for age of the patient versus ED clinical neurological grade, was not significant: slope = -0.09, $p = 0.96$.

8.3.3. Side effects of HBO and NBO treatment

There were relatively few side effects in this clinical series. Symptomatic pulmonary oxygen toxicity was defined as chest pain, tightness, cough or dyspnoea noted during or immediately after oxygen therapy. Vital capacity was not measured. Ear barotrauma was defined using the Edmonds classification (Edmonds et al 1992). Twelve of the hyperbaric treated patients noted some difficulty with clearing their ears. The side effects of treatment are outlined in table 8.5.

Table 8.5 Side effects from HBO and NBO treatment

Adverse effect	HBO Group n = 49 Data not recorded in 8	NBO Group n = 13 Data not recorded in 4
Ear barotrauma greater than grade 2 Edmonds classification	2	Nil
Myringotomy	1 (Comatose patient)	Nil
Symptomatic pulmonary oxygen toxicity	3	Nil Dryness and hoarse voice noted in 6/13
Seizures	Nil	Nil
Claustrophobia	Nil	Nil

8.4. Discussion

In this chapter, the enrolment of a prospective case series of CO poisoned patients is described in detail, and how the data from these patients is used for analysis in the chapters to follow. Almost 80% of the 66 patients were males. This was accounted for by the high number of males sustaining their CO poisoning from episodes of deliberate self-harm (76.9%). In the deliberate self-harm population, males made up 91%. My findings are similar to other Australian series of CO poisoning. Scheinkestel reported a population of 191 CO poisoned patients, 68.6% who were suicidal, and 81.7% were male (Scheinkestel et al 1999), and in Gorman's series, 51% were suicide attempts (Gorman et al 1992). There appears to be a difference in the demographics of Australian series compared with Weaver's study population from North America. Weavers group in 2002 also noted a high percentage of male patients (71%), however only 31% were suicide attempts.

Thirty-eight (61.3%) in the series had LOC, 20 had no LOC and for 4, the conscious state was unknown. Of the 24 who did not lose consciousness or in whom the situation was unknown, a further 9 had impaired cognitive or neurological function when assessed in the ED. Hence 47 (76%) had severe CO poisoning, according to the definition used by Scheinkestel et al (Scheinkestel et al 1999). Thirty out of 48 males lost consciousness and 8/14 females lost consciousness.

A statistically significant relationship was found between the duration of loss of consciousness and the ED clinical neurological grade. The longer the individual was unconscious, the more severe the neurological impairment when they reached the ED. This is likely to result from the individual's greater CO exposure to produce unconsciousness, plus any continuing exposure whilst unconscious, and possibly the effects of hypoxia due to compromised airway/breathing. No statistically significant relationship was demonstrated between the time delay to treatment and the ED neurological grade, or the patient's age and the ED neurological grade.

The accidental population, that had more females, also had greater numbers of younger individuals (teenagers and children). Our series identified a high-risk subgroup: 23 were males between the ages of 20 and 30, undertaking a potentially lethal method of self-harm. It is likely that the easy availability of motor vehicles to young adult males is a factor in the use of CO as a method of attempting suicide. The deliberate self harm group contrasts with those with accidental poisoning, where numbers were almost equally distributed between the sexes (12 male, 10 female).

In this case series, 3 individuals refused to enter the study. These are described in detail in chapter 14. An additional patient was referred nearly three weeks after his exposure to CO, and his clinical course is described in detail in appendix 18.7. On the 62 patients enrolled in the study protocol, 49 individuals were allocated to HBO treatment, and 13 received NBO. This uneven distribution was expected as patients were not randomized at entry. Fremantle Hospital received referrals of patients who were more severely poisoned, from all hospitals in Perth, for HBO treatment. Patients who were less severely poisoned, were treated at their local hospital. As a result the NBO treated group consisted of patients from Fremantle Hospital only.

Side effects of treatment were relatively few. Approximately on quarter of poisoned patients had difficulty with ear clearing, yet only 4% had significant ear barotrauma and one required a myringotomy whilst comatose. Symptomatic pulmonary oxygen toxicity occurred in 6% treated with HBO. Treatment with NBO without humidification caused symptomatic distress in nearly half the patients.

8.5. Conclusions

Sixty-six consecutive patients were identified for possible entry into this series, of which 62 patients (93.9%) were enrolled in the study. The study treatment protocol was precisely followed in 94% of patients, and only 3% were lost to follow-up. There were a high percentage of males, a high percentage of individuals exposed themselves to CO as an act of deliberate self-harm, and a high percentage lost consciousness. Duration of LOC correlated significantly with the severity of neurological impairment observed for patients at presentation in the ED. Delays to treatment and the patients' age did not correlate with their neurological status at presentation. Significant side effects of treatment were uncommon, and no oxygen toxicity seizures occurred.

9. CORRELATION OF COHb WITH ECO BREATHING AIR

9.1. Aim

To examine the relationship between COHb and mean ECO breathing air for non-smokers and smokers, and acutely poisoned patients.

9.2. Methods

The relationship between COHb and ECO was investigated in this chapter. Paired blood and breath samples (breathing air) were obtained from non-smokers, smokers, and poisoned patients. Measurements of CO offgassing were not undertaken and the volume of CO excreted was not measured, because the samples were measured at a single point in time.

Matched pairs of COHb and ECO samples were collected. From all of the acutely (<6 hours) poisoned patients. Poisoned subjects provided breath samples within approximately 30 – 60 minutes of their blood sample. During the period between samples, they were receiving 100% oxygen treatment.

Measurement of COHb was undertaken in the Department of Biochemistry at Fremantle Hospital, using spectrophotometry methods. The technique has been previously described (Katsumata et al 1981). Fifteen microlitres of blood were added to 5 ml of 0.1% sodium carbonate, followed by 5mg of sodium hydrosulphite. After mixing, 0.5ml of 1N sodium hydroxide was added and an absorbance spectrum recorded from 500 to 600 nm, using a solution of 0.1% sodium carbonate as a blank. Carboxyhaemoglobin was recorded by calculating the difference between the absorbance spectra. The test worked on the principle that the spectrum of Hb is modified by sodium hydroxide, and COHb is not. Its maximum accuracy was for a range of COHb = 8 - 22 percent. Katsumata reported 0.8 - 5.8 percent discrepancies compared with the oxygen electrode method (the gold standard at the time), for COHb levels in the range of 53.1 to 90.8 percent. The inaccuracy of the spectrophotometric test became greater, for higher levels of COHb. Katsumata did not evaluate the spectrophotometric method for lower levels of COHb, however graphs from the original paper suggested a linear relationship between absorbance spectra and the COHb across the range of 2.3% to 95.5% COHb (Katsumata et al 1981).

Measurement of ECO occurred in accordance with the methods outlined in chapter 6 of this thesis. The ECO recorded was the mean value determined over a 5-minute sampling period.

9.3. Results

9.3.1. COHb versus ECO breathing air - non-smoking controls

Twenty-three volunteers agreed to provide a blood sample for COHb at the same time as they provided ECO samples. There were 17 males and 6 females. Their mean age was 33.0 years (95% CI = 27.8 to 38.2). They had a mean COHb of 0.06% (0.0 to 0.15), and mean ECO breathing air = 1.3 ppm (95% CI = 0.8 to 1.8). Table 9.1 summarises the data.

Table 9.1 – Non-smoker ECO compared with COHb

Age	Sex	Non-smokers ECO (ppm)	Non-smokers COHb (%)
31	F	1	< 0.2
47	M	1	< 0.2
24	M	1	< 0.2
30	M	1	< 0.2
38	M	1	< 0.2
46	M	1	< 0.2
27	F	1	0.2
29	M	1	0.2
30	M	1	< 0.2
32	M	0	< 0.2
30	M	1	< 0.2
29	M	1	< 0.2
15	F	1	< 0.2
69	M	6	< 0.2
44	F	3	1.0
19	F	1	< 0.2
45	M	1	< 0.2
38	M	0	< 0.2
33	M	1	< 0.2
33	M	1	< 0.2
14	M	2	< 0.2
21	F	2	< 0.2
34	M	7	< 0.2

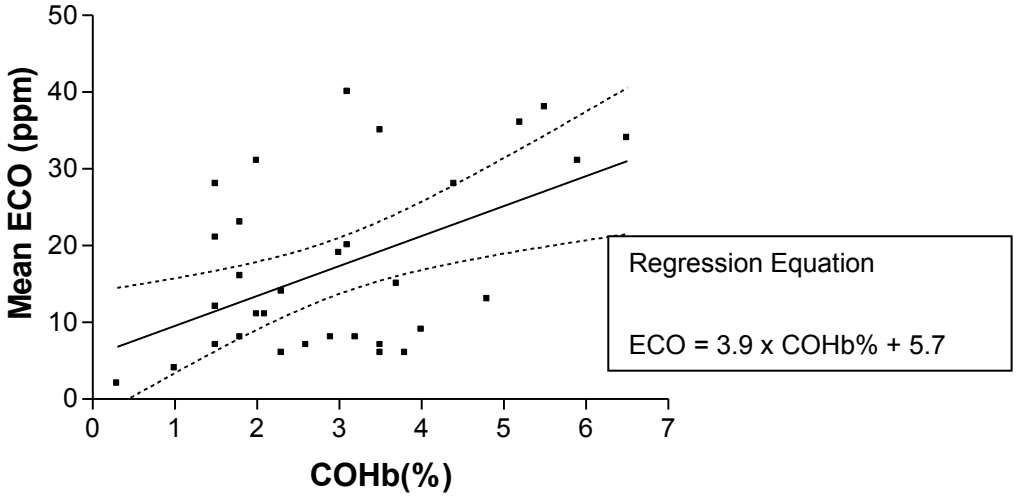
The ratio of ECO to COHb for three samples where it could be calculated was 4.3 ppm/% COHb.

As a result of the large number of samples (n=20) that had unrecordable COHb levels (< 0.2%), the regression curve was not calculated for this data.

9.3.2. COHb versus ECO breathing air - smokers

Forty volunteer smokers had a blood sample to measure COHb while ECO was measured breathing air. This sample consisted of 24 males and 16 females, mean age 29.6 years (95% CI = 25.4 to 33.8). They smoked an average of 15.1 cigarettes per day (95%CI = 12.0 to 18.2). Their mean COHb was 2.4% (95%CI = 1.8 to 3.0), and mean ECO breathing air was 14.7 ppm (95% CI = 11.0 to 18.4). Table 9.2 shows the matched pairs of ECO and COHb for the smoker control group breathing air. The results of this group are shown graphically in figure 9.1. The regression line is shown with 95% confidence limits.

Figure 9.1 ECO versus COHb in 32 smokers breathing air



There was a strong correlation between COHb and ECO for the smoker group. A value of r^2=0.25, p=0.003 was found. The gradient was 3.9 (95% CI 1.4 to 6.4). The regression line crossed the y axis at 5.7 (95% CI= -2.7 to 14.0).

Table 9.2 ECO breathing air compared with COHb for smokers

Age	Sex	Number of cigarettes per day	ECO (ppm)	COHb (%)
59.0	F	30	20	3.1
44.0	F	40	31	5.9
32.0	F	30	28	4.4
50.0	F	6	11	2.0
30.0	M	15	38	5.5
37.0	M	20	40	3.1
39.0	M	15	14	2.3
20.0	M	25	31	2.0
20.0	M	9	35	3.5
36.0	M	30	36	5.2
43.0	M	15	16	1.8
16.0	M	2	3	< 0.2
15.0	M	10	11	2.1
60.0	M	20	34	6.5
16.0	M	20	15	3.7
14.0	M	6	2	< 0.2
16.0	M	1	4	< 0.2
16.0	M	10	12	1.5
14.0	M	10	23	1.8
15.0	F	7	9	< 0.2
40.0	M	15	28	1.5
15.0	F	2	2	< 0.2
13.0	F	2	4	< 0.2
18.0	F	20	21	1.5
14.0	F	3	8	< 0.2
37.0	F	10	4	1.0
44.0	F	14	7	2.6
25.0	F	15	6	3.8
42.0	M	30	7	3.5
32.0	F	10	8	2.9
34.0	M	5	6	2.3
44.0	M	10	8	3.2
31.0	F	20	8	1.8
39.0	M	15	7	1.5
30.0	F	8	19	3.0
19.0	F	5	1	< 0.2
17.0	M	20	2	0.3
37.0	M	30	6	3.5
30.0	M	25	9	4.0
32.0	M	25	13	4.8

The ratio of ECO (ppm) breathing air, to COHb (%) was calculated using the 32 matched pairs with COHb > 0.2. The ratio breathing air was 6.4 ppm/% COHb (95% CI = 4.9 to 8.0).

9.3.3. COHb versus ECO breathing air - acutely poisoned patients

Mean ECO samples were recorded for 12 acutely poisoned patients (exposure < 6H previously) presenting to Fremantle Hospital ED, who were referred for HBO during the course of the study. These consisted of 1 female and 11 males (mean age 34.7 years, 95% CI = 28.8 to 40.5). All were due to suicide attempts. Their mean COHb levels were 16.3 % (95% CI 9.5 to 23.2), and mean ECO (air) was 66.2 ppm (95% CI = 30.5 to 101.9). Nine were smokers and three were non-smokers. There was no significant difference between the ECO for smokers versus non-smokers in this poisoned sample (p=0.26 using an unpaired t test). The results are tabulated in table 9.3.

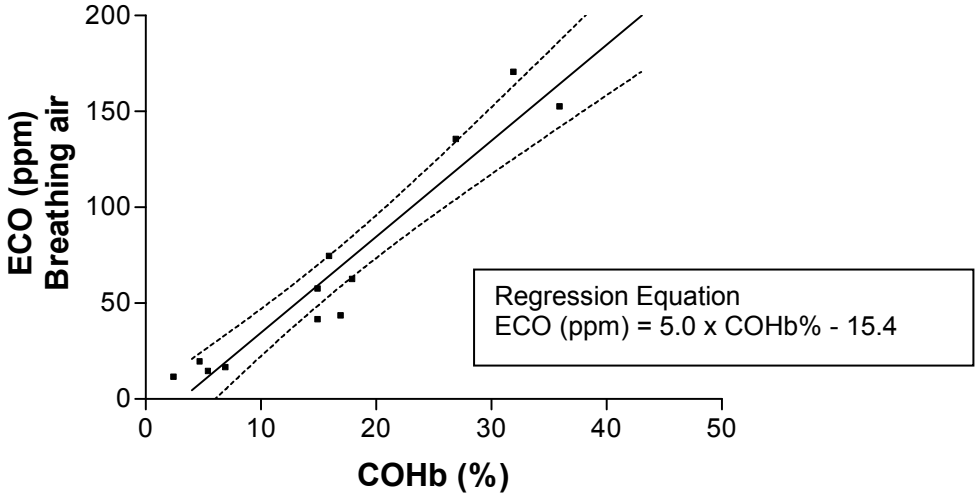
Table 9.3 COHb compared to ECO breathing air, and demographics of the acutely poisoned patients

Subject	Age	Sex	Smoker?	ECO (ppm) Breathing air	COHb (%)
1	44	male	yes	19	4.8
2	24	male	yes	74	16.0
3	30	male	yes	135	27.0
4	26	male	yes	14	5.5
5	48	male	no	41	15.0
6	41	male	yes	43	17.0
7	36	male	yes	152	36.0
8	42	male	yes	16	7.0
9	19	female	no	62	18.0
10	41	male	no	57	15.0
11	27	male	yes	170	32.0
12	38	male	yes	11	2.5
Mean ± SD	**34.7 ± 9.2**			**66.2 ± 56.2**	**16.3 ± 10.8**

A ratio of ECO (ppm) to COHb (%) was determined for these matched pairs. This ratio was 3.7 ppm/% COHb (95% CI 3.1 to 4.4).

A graph showing the relationship between ECO and COHb for the poisoned patients is shown below in figure 9.2. The correlation between ECO and COHb was strong, with r^2=0.92, p < 0.0001. The plot showed a gradient of 5.0 ppm/% COHb (95% CI = 4.0 to 6.0). The regression line crossed the y-axis at –15.4 (95% CI = -35.1 to 4.2).

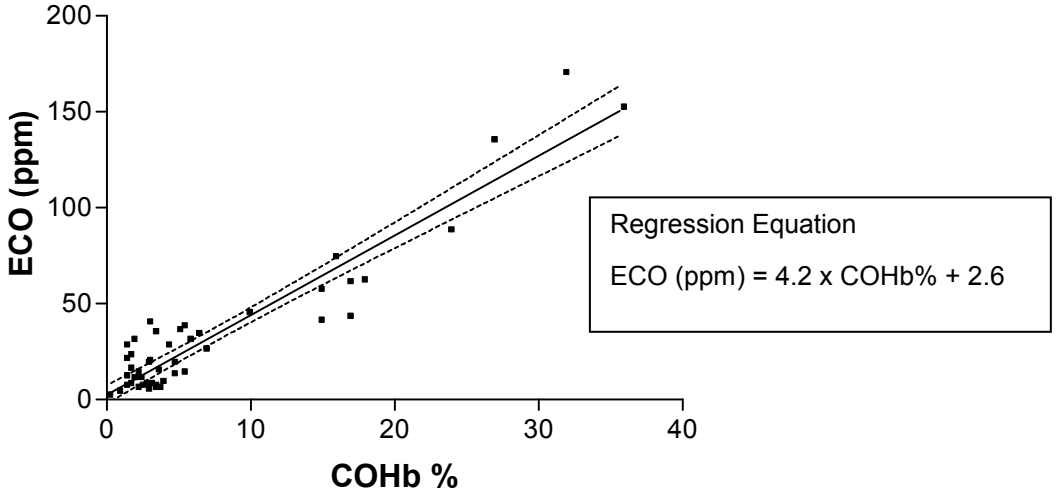
Figure 9.2 COHb correlated with ECO breathing air for 12 acutely poisoned patients



9.3.4. Pooled Data – COHb correlated with ECO for smokers and poisoned patients

A total of 44 samples were obtained from the two groups breathing air with matched ECO / COHb samples. Data from non-smokers was not used due to the high number with unrecordable COHb levels. The following graph was produced, pooling all available matched pairs of ECO (breathing air), and COHb levels (figure 9.3).

Figure 9.3 ECO correlated with COHb – pooled data smokers and acutely poisoned patients



These provided a strong correlation between ECO readings and percent COHb $R^2 = 0.88$, $p<0.0001$. The gradient of the relationship was 4.2 (95% CI 3.7 to 4.6 and it crossed the y axis at 2.6 (95% CI – 2.3 to 7.4). The confidence limits of this "y" intercept encompassed zero, indicating that the positive "y" intercept was not significantly different from zero.

Data from the smokers and acutely poisoned populations are summarised in table 9.4. The pooled data demonstrates a linear regression gradient of 3.89 ECO ppm / COHb %. The ratio using matched pairs was 5.69 ECO ppm / COHb %.

Table 9.4 Paired ratios calculated for the relationship between ECO (ppm) and COHb (%) breathing air

Population Sample (n)	**Relationship between ECO and COHb Mean (95% CI)**	
	Linear Regression Gradient ECO ppm/COHb %	**Matched pair ratios ECO ppm/COHb %**
Smokers (32/40)	3.9 (1.4 to 6.4)	6.4 (4.9 to 8.0)*
Poisoned patients (12/12)	5.0 (4.0 to 6.0)	3.7 (3.1 to 4.4)
Pooled Smoker and Poisoned (44/52)	4.2 (3.7 to 4.6)	5.7 (4.5 to 6.9)

* Statistically significant difference from poisoned patients (p=0.003, unpaired t test).

9.4. Discussion

The data presented suggest that baseline levels of ECO and COHb in non-smokers are very low. A clear relationship between the ECO and COHb levels could not be established in non-smokers. The most likely reason for this that observed COHb levels were near or below the limits of resolution each of the tests. In particular, the spectophotometric method used by the Fremantle Hospital Department of Biochemistry for determining COHb has limitations below COHb levels of 2.3% that were outlined in the methods (Katsumata et al 1981). It is possible that CO breath analysis is more accurate at low levels of COHb, due to its finer resolution, because ECO data was available for all 23 non-smokers whereas only 3/23 COHb levels were recordable. It would have been preferable to use co-oximetry to measure COHb, because it has a higher degree of precision at COHb < 2.5%, than spectrophotometric methods (Widdop 2002). Widdop reviewed the methods of analysis of carbon monoxide, and noted that compared to a gas-chromatographic reference, most co-oximeters delivered an accuracy of 0.1 to 0.16% for COHb < 2.5%. This would have allowed more effective correlation between ECO and COHb. At levels less than 2.3% COHb, the spectrophotometric method was regarded as unreliable, and potentially unrecordable, with errors up to 0.4% (Katsumata et al 1981). From my data, a COHb level of 2.3% corresponded to ECO ~ 9-13 ppm. This created a major problem in interpreting the relationship between ECO and COHb at low levels of COHb.

In smokers there was a strong correlation between ECO and the COHb levels, and a strongly positive correlation was also observed for the 12 patients who satisfied the criteria of acute poisoning (<6 hours since rescue).

Using the pooled data for smokers and poisoned individuals, ECO (ppm) ranged between 3.9 and 5.7 times the COHb (%) reading for the smokers and poisoned subjects. Smokers had a less steep gradient for their linear regression curves than poisoned patients. There is considerable overlap of the 95% confidence limits however, and the difference is not statistically significant. However this was not the case for the matched pair ratio calculations. Smokers had a significantly higher ECO ppm/COHb % ratio than poisoned subjects. Differences in observed ratios for the three populations summarized in table 9.4 may reflect CO accumulation in other body stores, where CO is dissolved or bound to respiratory pigments other than haemoglobin. It may also be explained by delays in sampling and errors due to experimental method (including the biochemical technique for measuring COHb). The values determined for ECO ppm/ % COHb gradients and ratios are very close to that stated by Bedfont

in the manual for their CO analyser, 5.0 ppm/% COHb (Bedfont Scientific Limited, undated). This supports the validity of the apparatus used in my research. A literature search identified one case report correlating CO in the breath, with COHb (Wallace 1998). Wallace's reported value of 180 ppm CO corresponded to a COHb = 26% (a ratio of 6.9 ppm/% COHb) was higher than the values determined in this chapter.

The tiered referral system and regional hospital structure in the City of Perth, WA (figure 8.2) created difficulty with early ECO data collection from poisoned patients. Patients were initially treated at their district hospital, and transferred to its "parent" tertiary centre, followed by referral to the State Hyperbaric Facility at Fremantle Hospital. This sometimes resulted in unavoidable delays of many hours, during which time the poisoned individual had prolonged periods of oxygen treatment. It was not possible to obtain early ECO readings in many individuals. The only practical way of achieving this would be measurement of ECO in the prehospital setting and correlate the reading with the individual's clinical status. This was beyond the scope of this study. It was likely that treatment with high flow or 100% oxygen before sampling may have acted as a confounder by removing CO from the patient, hence affecting the CO breath reading. This would have led to artificially low ECO values for the degree of poisoning noted by the patients, and is recognised as a major flaw in this study. Another method of estimating acute ECO values is to perform retrospective extrapolation of ECO values to the time of the rescue, using half-life nomograms, based on the time since rescue and current ECO value. Again this has potential for significant errors, due to lack of precise data regarding oxygen dose during prehospital and primary hospital treatment, and also the fact that individual half-lives may vary between individuals (Myers et al 1984). If my study were to be repeated, then contemporaneous sampling of ECO and COHb at the time of rescue would be essential strengthen the validity of any conclusions attempting to correlate ECO with clinical severity of poisoning.

In an attempt to minimise this confounding influence, acutely poisoned patients were studied in this chapter. These were restricted to those who reached Fremantle ED less than 6 hours post exposure to CO. Even these patients had COHb blood samples followed by up to one hour of 100% oxygen treatment before ECO measurements were taken, due to delays in the investigators arriving at Fremantle Hospital. This group provided blood samples for COHb, followed by ECO measurements within 30 to 60 minutes. During the time delay, the 100% oxygen treatment continued to remove CO. This was a significant source of potential error in the study. Unfortunately the practical realities of

after-hours call back coupled with logistic issues dealing with treating the poisoned patient contributed to delays. For after-hours presentations, a time delay occurred when the author or assistants were called into Fremantle ED. The ECO readings for this group were lowered by ongoing oxygen treatment during the time delay to sampling. This is the most likely reason why poisoned individuals had significantly lower ECO/COHb ratios compared with smokers.

The regression line for smokers and poisoned patients crossed the y-axis at 2.6 ppm (CO = 2.6 ppm when COHb = 0). Despite a positive value for the "y" intercept, the confidence intervals crossed zero which meant that this value was not significant. By applying the Coburn-Forster-Kane equation, there cannot be ECO without a small amount of COHb present (Coburn et al 1965. In Coburn et al's original work, a measured ECO corresponded to a COHb of 0.39%. Hence there is a significant potential source of error resulting from the limits of the biochemical test for COHb. Undetectable values were often reported as < 0.2%, when they may have been up to 0.4% higher (Katsumata et al 1981, Widdop 2002).

As a result of potential flaws in my methodology, further work is needed using the more sensitive co-oximetry to measure blood COHb, and more precisely time-matched samples of ECO and COHb. Co-oximetry was not available at the time of the study. The poor sensitivity of the COHb biochemical measurements at low levels may have affected the correlation between the ECO and percentage COHb. More sensitive equipment may also have allowed more meaningful data to be collected from non-smokers.

9.5. Conclusions

These data suggest that there is a strong positive linear relationship between the ECO and COHb. This was observed for smoker controls and poisoned patients as well as the pooled data. The limits of resolution of the biochemical test to detect COHb prevented meaningful data from non-smokers. The gradients and ratios for the ECO (ppm) versus COHb (%) for smokers and poisoned patients were consistent with data from Bedfont, but less that the values determined by Wallace. Available data also suggest that the ECO reading may be more sensitive in detecting CO than the biochemical test for COHb. Expired CO was detectable in all non-smokers, however COHb could be detected using the biochemical test in only a minority of non-smokers. As a result of potential flaws in my methodology, further work is needed using the more sensitive co-oximetry to measure blood COHb, and more precisely time-matched samples of ECO and COHb.

10. ECO CORRELATED WITH COHb BREATHING AIR, NBO AND HBO

Introduction

It has long been demonstrated that an increase in inspired oxygen partial pressure (P_IO_2) increases tissue oxygen delivery, and results in faster CO removal from the blood, and shorter elimination half-lives (Pace et al 1950, Peterson and Stewart 1970). As a result, most authorities recommended that victims of CO poisoning receive 100% oxygen treatment in the emergency setting. HBO further increases alveolar, blood and tissue oxygen partial pressure. It was expected therefore, it would be possible to demonstrate increases in ECO (reflecting rate of elimination) when individuals were exposed to air, NBO and HBO.

10.1. Aim

The aim was to measure ECO and correlate it with COHb in environments of three inspired oxygen partial pressures. Oxygen partial pressures selected were the rescue environment, air at 1 ATA (P_IO_2 = 21.2 kPa) and those used in treatment; NBO at 1 ATA, (P_IO_2 = 101.3kPa) and hyperbaric oxygen at 2.8 ATA (P_IO_2 = 284 kPa).

10.2. Methods

The same 12 acutely poisoned patients who provided data in chapter 9 were studied. Expired CO measurements were taken from the patients within 6 hours of their CO exposure. The first samples taken in the ED reflected the initial ECO measurements breathing air (P_IO_2 = 21.2kPa) and 100% oxygen (P_IO_2 = 101.3kPa). Eight of the 12 patients then had a second set of ECO and COHb measurements performed close to the time of entry to the Hyperbaric Chamber. Four of the patients were transferred in less than 1 hour of arrival in the ED, and hence had only a single set of samples for COHb and ECO breathing air and oxygen.

After taking the blood sample for COHb there was a variable delay while the researcher or assistant attended the ED to measure ECO. Mean ECO was measured over 5-minute periods performed in air and NBO in the ED. The same process was followed when the patient was transferred for HBO treatment. Patients required 5-10 minutes after each change of P_IO_2, to allow ECO values to stabilise

before sampling commenced. The usual sequence of sampling was ECO breathing 100% oxygen followed by air, because the patients were receiving NBO treatment at the time. There was a longer delay before the HBO sample was taken, because pressurisation was required. Hence there were two sets of data from the patients:

(i) Matched COHb, and ECO breathing air and NBO in the ED, and

(ii) Matched COHb, and ECO breathing air, NBO just before entry to the hyperbaric chamber and HBO just after pressurisation to 2.8 ATA.

Expired CO measurements were collected as previously described in chapter 6, in order to study the effect of supplemental oxygen on ECO.

Expired CO breathing air and NBO was measured within one hour of the blood sample for COHb. The COHb samples for the HBO group were taken as they left the ED for the Hyperbaric Unit, or within the Hyperbaric Unit prior to compression. Time delays between samples were recorded to the nearest half-hour. There may have been up to 30 to 60 minutes of time delay before the matched ECO samples for some patients.

The RMV was recorded in this chapter of the research, because it permitted the calculation of CO offgassing in ml/minute for the three P_IO_2 environments, using the formula:

CO offgassing mL/min = mean [ECO] ppm x RMV L/min x 1000 ml/L

Measurement of offgassing was important because sampling from hyperbaric treated patients occurred after the exhaled gas had expanded during depressurisation to 1 ATA, hence increasing its volume.

The measurements of ECO (breathing air, 100% oxygen then HBO), were often separated by up to one hour after COHb sampling. This was longer than anticipated, because time was required for the P_IO_2 to equilibrate, and also the logistics of moving the patient into the Hyperbaric Unit, and pressurising the chamber.

10.3. Results

Expired CO and COHb breathing air and NBO in the ED

The study patients all had moderate severity CO poisoning, but were conscious and cooperative at the time of sampling.

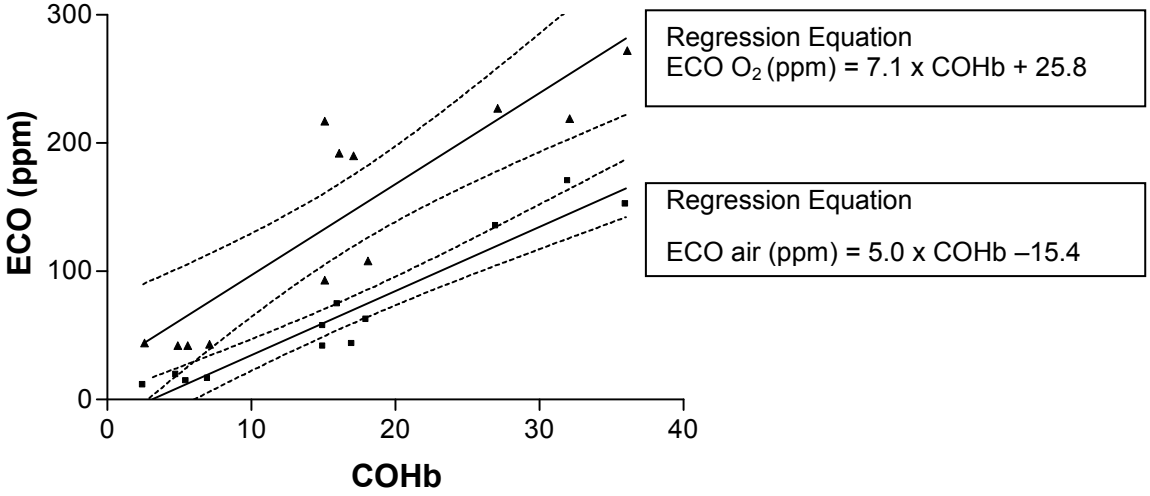
Table 10.1 shows all of the matched values for COHb and ECO breathing air and oxygen. The acutely poisoned patients at the time of sampling had a mean COHb = 16.3% (95% CI = 9.5 to 23.2), and ECO readings breathing air, 66 ppm (95% CI = 30.5 to 101.9), and ECO breathing oxygen, 141.7 ppm (95% CI= 86.4 to 197.1).

Table 10.1 Poisoned patient matched samples of ECO for poisoned patients breathing air and oxygen, versus COHb

Origin	Sex	Age	Acute ECO breathing air (ppm)	Acute ECO breathing O2 (ppm)	Acute COHb (%)
Poisoned	m	44	19	43	4.8
Poisoned	m	24	74	193	16.0
Poisoned	m	30	135	228	27.0
Poisoned	m	26	14	43	5.5
Poisoned	m	48	41	94	15.0
Poisoned	m	41	43	191	17.0
Poisoned	m	36	152	273	36.0
Poisoned	m	42	16	44	7.0
Poisoned	f	19	62	109	18.0
Poisoned	m	41	57	218	15.0
Poisoned	m	27	170	220	32.0
Poisoned	m	38	11	22	2.5
Mean for Poisoned		34.7	66	142	16.3
Range		19 to 48	11 to 170	43 to 273	2.5 to 36.0
Lower 95%CI		28.8	31	86	9.5
Upper 95%CI		40.5	102	197	23.2

The median time delay between COHb and ECO samples was 60 minutes. The ECO breathing oxygen was significantly greater than the ECO breathing air ($p < 0.0001$). In the above table, the mean ratio for ECO breathing air / COHb was 3.9 ppm/% (95% CI = 3.3 to 4.4). Breathing oxygen, the mean ratio of ECO/COHb was 9.5 ppm/% (95% CI= 7.1 to 11.9). The mean ECO breathing oxygen was 2.6 times the mean ECO breathing air (95% CI = 1.9 to 3.2). The relationship between ECO breathing oxygen and ECO breathing air is shown in figure 10.1. Air data from chapter 9 is repeated here to allow comparison between ECO breathing air and oxygen.

Figure 10.1 Expired CO breathing air and NBO versus COHb for poisoned subjects at presentation



A significant linear relationship between ECO and COHb was noted breathing air ($r^2 = 0.95$ $p<0.0001$), and oxygen ($r^2 = 0.92$, $p<0.0001$). The gradient of ECO vs COHb breathing air was 5.0 ppm/% (95% CI = 4.0 to 6.0), and y intercept – 15.4 ppm (-35.1 to 4.2). The gradient of ECO vs COHb breathing oxygen was 7.1 ppm/% (95% CI = 4.4 to 9.8), and y intercept 25.8 ppm (95% CI -26.2 to 77.7). The 100% oxygen regression slope was 1.4 times the air regression slope in this group of patients.

Expired CO samples and COHb breathing Hyperbaric Oxygen

Table 10.2 shows patient ECO samples breathing air, NBO and HBO, taken when poisoned patients were transferred for HBO treatment. Four of the patients had their COHb and ECO breathing air and oxygen measured in the ED just before transfer to the hyperbaric facility These four patients only had a single COHb sample and single ECO samples breathing air and oxygen. They are marked with an asterisk* in the table. In the table the ratios of ECO and CO offgassing breathing NBO are compared with breathing air, and HBO ECO and CO offgassing are compared with NBO. These are highlighted as grey backgrounds to the columns.

Table 10.2 COHb, ECO, CO offgassing measurements, and ratios for 12 poisoned subjects breathing air, NBO and HBO at 2.8ATA.

			Values Measured in Air			Measurements in NBO. Ratios show NBO ECO and offgassing values compared to air values					Measurements in HBO. Ratios show HBO ECO and offgassing values compared to NBO values				
Subject Number	Age	COHb Pre HBO	ECO in Air ppm	RMV (L)	CO offgas in air ml/min	ECO in NBO ppm	RMV (L)	CO offgas in O2 ml/min	Ratio ECO O2/air ppm	Ratio CO offgas O2/air ml/min	ECO in HBO ppm	RMV in HBO (L)	CO offgas in HBO ml/min	Ratio ECO In HBO to NBO ppm	Ratio CO offgas in HBO to NBO ml/min
A034	44	*4.8	19	6.7	0.13	43	7.6	0.33	2.3	2.6	53	19.9	1.05	1.2	3.2
B072	24	1.5	9	10.1	0.09	30	10.9	0.33	3.3	3.6	32	34.7	1.11	1.1	3.4
D042	30	*5.5	14	7.4	0.10	43	10.7	0.46	3.1	4.4	45	35.5	1.60	1.1	3.5
D428	26	2.0	4	11.7	0.05	16	12.9	0.21	4.0	4.4	14	37.3	0.52	0.9	2.5
E024	48	3.0	10	11.1	0.11	46	8.5	0.39	4.6	3.5	40	32.2	1.29	0.9	3.3
E050	41	1.0	4	6.3	0.03	150	9.8	0.15	3.8	5.8	16	41.5	0.66	1.1	4.5
E200	36	2.0	7	7.3	0.05	26	11.3	0.29	3.7	5.8	36	24.8	0.89	1.4	3.0
G425	42	*7.0	16	5.8	0.09	44	6.5	0.29	2.8	3.1	44	17.0	0.75	1.0	2.6
G714	19	Not Recorded	1	5.6	0.01	3	9.0	0.03	3.0	4.8	3	34.3	0.10	1.0	3.8
H072	42	2.2	5	6.8	0.03	28	8.2	0.23	5.6	6.6	19	36.0	0.68	0.7	3.0
J723	27	4.0	6	16.3	0.10	22	21.8	0.48	3.7	4.9	38	36.8	1.40	1.7	2.9
K217	38	*2.5	11	6.4	0.07	22	11.3	0.25	2.0	3.5	30	26.4	0.79	1.4	3.2
Mean	**34.7**	**3.2**	**8.8**	**8.5**	**0.07**	**28.2**	**10.7**	**0.29**	**3.5**	**4.4**	**30.8**	**31.4**	**0.90**	**1.1**	**3.3**
Lower 95% CI	28.9	2.0	5.4	6.4	0.05	19.5	8.2	0.21	2.9	3.6	21.4	26.5	0.64	0.9	2.9
Upper 95% CI	40.6	4.5	12.3	10.5	0.10	36.8	13.2	0.37	4.1	5.2	40.3	36.2	1.17	1.3	3.6

* = Samples taken in ED just before transfer to Hyperbaric Chamber

At the time of HBO treatment, the poisoned patients had a mean COHb reading of 3.2 %, mean ECO (air) was 8.8 ppm, ECO (O_2) was 28.2 ppm, and ECO (HBO) was 30.8 ppm. Initially mean ECO values breathing air in the ED were 66.2 (table 10.1). This difference was statistically significant (p = 0.005). The fall in COHb from an initial mean of 16.3% (95%CI = 2.5 to 36.0) to a pre chamber mean of 3.2% (95%CI = 2.0 to 4.5) was also statistically significant (p=0.0009). These values confirmed that a considerable amount of their CO had been removed before commencing HBO treatment. The mean delay from study entry to HBO treatment was 2.6 hours.

Using data from table 10.2, ECO breathing NBO was compared to ECO breathing air. The mean ratio was 3.5 (95% CI = 2.9 to 4.1). A higher value was obtained when RMV was taken into account, measuring CO offgassing in ml/minute. The mean ratio for NBO/Air CO offgassing was 4.4 (95% CI = 3.6 to 5.2). A ratio of 4.8 would be expected if CO excretion had a linear correlation with P_IO_2. (= 1.00 ATA / 0.21 ATA). The second ratio is closer to 4.8 and the confidence limits overlap this.

Mean CO offgassing breathing air was 0.07 ml/min (95%CI = 0.05 to 0.10). Mean CO offgassing in NBO just prior to HBO, was 0.3 ml/min (95% CI = 0.2 to 0.4). Mean initial CO offgassing in HBO was 0.9ml/min (95% CI = 0.6 to 1.2). CO offgassing was significantly higher in NBO than air, ($p<0.0001$). The CO offgassing in HBO was significantly higher than NBO, ($p < 0.0001$). Expired CO concentration measured during HBO treatment was not significantly different from ECO when breathing NBO (p=0.22). The mean ECO ratio for HBO/NBO was 1.1 (95% CI = 0.9 to 1.3). Because the HBO measurements were taken outside the chamber, the RMV breathing HBO was significantly greater than NBO (table 10.3). Exhaled gas expanded by a factor of 2.8 as it moved to the lower pressure outside the chamber of 1ATA. The CO offgassing in HBO was 3.3 times that of NBO (95% CI = 2.9 to 3.6). This value was higher than the expected ratio of 2.8, if CO excretion was exactly in proportion to P_IO_2.

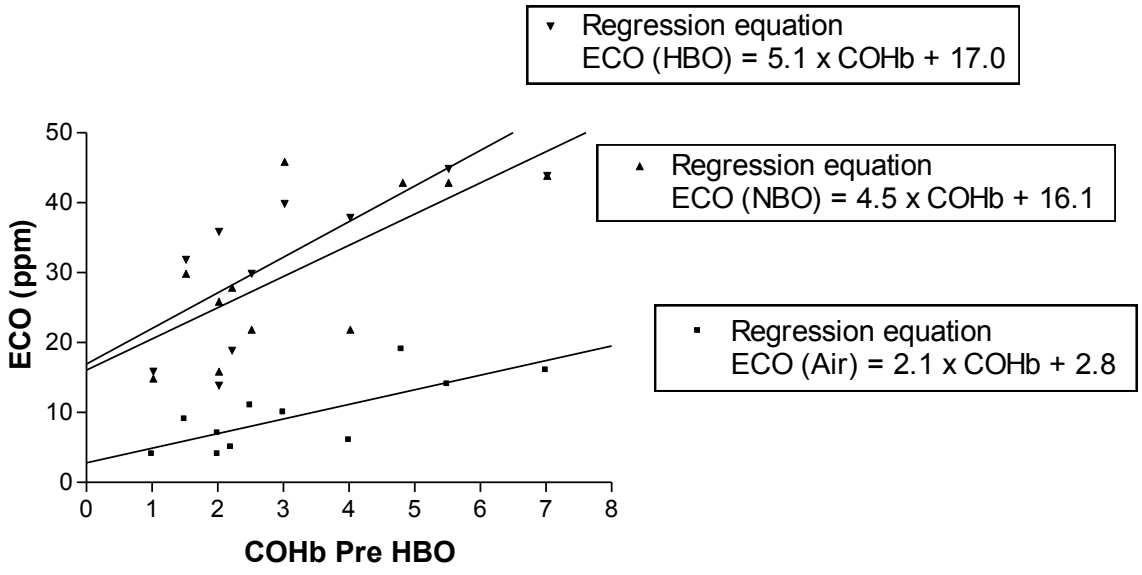
There were significant differences in RMV when comparing the 12 patients breathing air, NBO and HBO, as summarized in table 10.3.

Table 10.3 Comparison of RMV for different P_IO_2 environments

Inspired Gas (P_IO_2)	Mean RMV (L) (95% CI)	Comparison	Mean of differences (95% CI)	P Value
Air at 1.0 ATA (21.4 kPa)	8.5 (6.4 to 10.5)	**Air vs NBO**	-2.2 (-3.7 to -0.8)	0.006
		Air vs HBO	-22.9 (-27.3 to -18.5)	< 0.0001
NBO = 1.0 ATA (101.3 kPa)	10.7 (8.17 to 13.2)			
		NBO vs HBO	-20.7 (-25.1 to –16.2)	< 0.0001
HBO = 2.8 ATA (284 kPa)	31.4 (26.5 to 36.2)			

ECO readings were plotted against the COHb for the twelve patients in air, NBO and HBO. The results are shown below in figure 10.2. The 95% confidence limits were removed for clarity. The slope of the ECO/COHb regression line increases as the P_IO_2 increased in figure 10.2. There were significant linear relationships between ECO and COHb breathing air, NBO and HBO.

Figure 10.2 ECO breathing air, NBO and HBO compared with COHb for 12 acutely poisoned patients just prior to hyperbaric chamber entry



The correlation between COHb and ECO for each P_IO_2 was statistically significant. The correlation coefficients, slopes and y intercepts of the above graph are summarised in table 10.4. The "y" intercepts for the regression lines were all positive. Breathing NBO and HBO the "y" intercept 95% confidence limits were also positive. This implied that breathing oxygen, it was possible to excrete carbon monoxide in the breath when the COHb was undetectable. The y intercept confidence limits breathing air crossed zero.

Table 10.4 Summary of correlation between ECO and COHb for 12 poisoned subjects breathing air, NBO and HBO (relates to figure 10.2)

Relationships for ECO vs COHb	**Correlation Coefficient and p value**	**Slope of Curve (95% CI)**	**"y" Intercept (95% CI)**
Breathing air	0.6 (p = 0.005)	2.1 (0.8 to 3.4)	2.8 (-1.9 to 7.5)
Breathing NBO	0.5 (p = 0.013)	4.5 (1.2to 7.7)	16.1 (4.0 to 28.1)
Breathing HBO	0.6 (p = 0.008)	5.1 (1.7 to 8.4)	17.0 (4.6 to 29.3)

A further graph was plotted for the volume of CO offgassed in each of the treatment environments, compared with the COHb at chamber entry (Figure 10.3). This demonstrated that for a given COHb, the greatest amount CO was offgassed in HBO, and the least amount in air. There was a statistically significant increase in offgassing comparing air with NBO and HBO ($p<0.0001$, repeated Measures ANOVA).

Figure 10.3 Carbon monoxide offgassing versus prechamber COHb for individuals breathing air, NBO and HBO

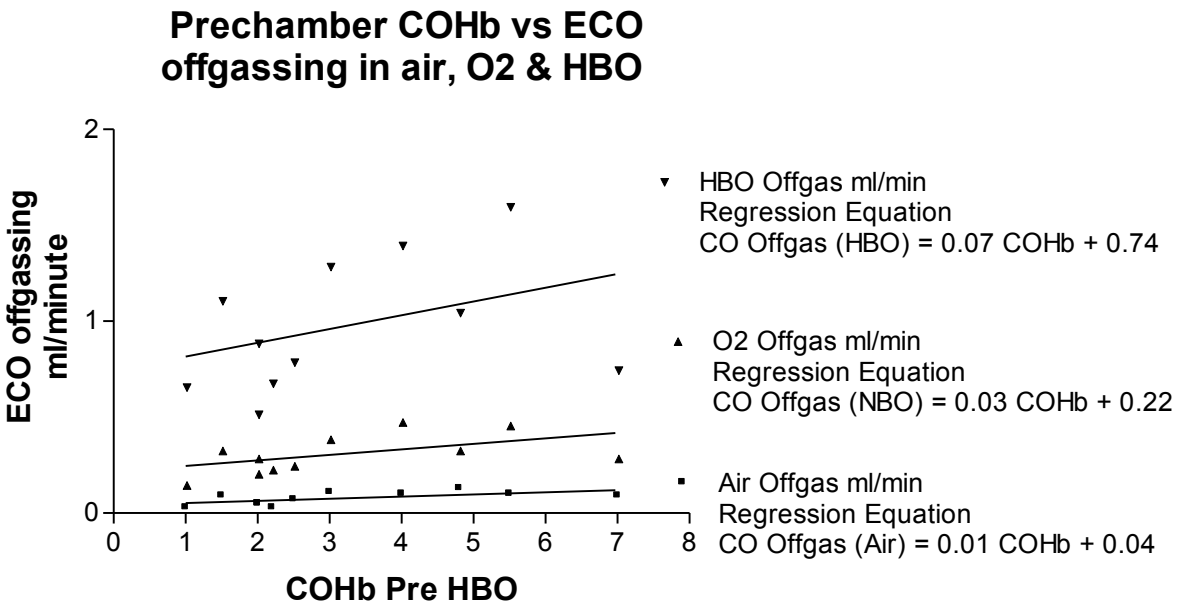


Table 10.5 shows ECO samples from the 12 poisoned patients were measured breathing air, NBO and HBO, taken close to the time of their entry to the hyperbaric chamber. These were compared to COHb levels taken close to the time of their entry to the hyperbaric chamber. The mean ratio of ECO (air) to COHb was 3.3 ppm/% (95% CI = 2.4 to 4.1). For ECO breathing NBO, the ratio was 12.2 ppm/% (95% CI = 7.9 to 16.5), and for ECO breathing HBO, the ratio was 11.9 ppm/% (95% CI = 8.7 to 15.2).

Table 10.5 Ratios of ECO/COHb for poisoned patients breathing air, NBO and HBO (samples taken close to the time of entry to the hyperbaric chamber)

COHb Pre HBO	Ratio ECO air / COHb	ECO breathing air ppm	Ratio ECO NBO / COHb	ECO breathing O2 ppm	Ratio ECO HBO / COHb	ECO breathing HBO ppm
4.8	4.0	19	9.0	43	11.0	53
1.5	6.0	9	20.0	30	21.3	32
5.5	2.6	14	7.8	43	8.2	45
2.0	2.6	4	8.0	16	7.0	14
3.0	3.3	10	15.3	46	13.3	40
1.0	4.0	4	15.0	15	16.0	16
2.0	3.5	7	26.0	15	18.0	36
7.0	2.3	16	6.3	44	6.3	44
0.0		1		3		3
2.2	2.3	5	12.7		8.6	19
4.0	1.5	6	5.5	22	9.5	38
2.5	4.4	11	8.8	22	12.0	30
Mean Ratios	**3.3**		**12.2**		**11.9**	

In the above table, paired ECO values breathing NBO and HBO were not significantly different using a paired t test ($p = 0.18$). Both the NBO and HBO ECO readings were significantly different from the ECO breathing air (For NBO and HBO, $p < 0.0001$).

10.4. Discussion

A linear relationship was observed for ECO breathing air and COHb for poisoned patients. This linear relationship between ECO and COHb was preserved when the individuals breathed NBO, however there were some important differences in the regression line gradients and y intercepts.

Breathing NBO, gradients for ECO versus COHb were significantly higher, than breathing air. This indicated that for a given COHb, raising the P_IO_2 increased the exhaled concentration of CO. Measured in the ED, breathing NBO had the effect of increasing the ECO/COHb gradient by a factor of 1.4, compared with breathing air. This was lower than the increase in gradient of 2.14 observed when samples were collected just before HBO treatment. Sample timing may have also affected the ECO values breathing air in the poisoned patients. For the poisoned individuals, air samples were taken during a 5 - 10 minute break from 100% oxygen treatment. In hindsight, this break may not have been long enough, and alveolar PO_2 may have still been elevated at the time the "air" sample was taken. Expired CO may have remained higher as a result of prior oxygen treatment. Delays between COHb sampling and ECO sampling may also have affected ECO measurements, because the patients were receiving active NBO treatment at the time. The author received assistance from other to collect data from some of the after hours patients, abd the problem of time matching of samples became apparent only after the data statered to be analysed. The main problem was that some assistants relied on only the ED COHb sample, rather than repeating the sample at the hyperbaric unit. This led to delays of up to 1 hour between COHb and ECO, which is a potential major flaw in the study.

It is of interest that neither increase in regression line gradients was in proportion to the magnitude of increase in P_IO_2. When matched pair ECO/COHb ratios were calculated, higher values were obtained than the regression line gradients. ECO breathing oxygen increased by a ratio of 3.5 compared with air. The actual excretion of CO (ml/minute offgassing) increased by a factor of 4.4 when respiratory minute volume was taken into account. The 95% confidence limits overlapped the expected value of 4.8, which would apply if CO excretion were in direct proportion to the P_IO_2. The findings of this chapter suggests excretion of CO from the lungs is a linear function of P_IO_2.

In the poisoned patients studied, a statistically significant linear relationship was observed for between ECO and COHb, when breathing air, NBO and HBO. The slope of the regression line when breathing air for the poisoned patients was lower than expected (gradient = 2.1 ppm/%), compared to data

obtained in chapter 9. This also may have been affected by time delays between COHb blood samples and the ECO sample, with oxygen treatment lowering ECO due to ongoing removal of CO. Differences in CO elimination rates between individuals would have also affected this result. Longer delays would have resulted in greater discrepancies between ECO values compared with COHb, if individual excretion rates were different.

When breathing NBO, the ECO/COHb gradient increased by a factor of 2.1 to 4.5 ppm/%. This was lower than expected, especially when compared to data from the acute samples.

Mean ECO values breathing HBO were not significantly different from those measured breathing NBO, and there was considerable overlap of the 95% confidence limits. This implied that the ECO *concentration* in HBO was not increased compared with NBO despite the elevated P_IO_2 in HBO. Both HBO and NBO provided 100% oxygen. What did change was the volume of CO excreted when patients were treated with HBO. In this study, ECO samples from the hyperbaric environment were measured at 1 ATA outside the hyperbaric chamber. The ECO concentration (in ppm) would have been the same inside the chamber; however the exhaled gases would have been 2.8 times *more dense*. When depressurised to the measuring equipment outside the chamber, according to Boyle's Law, CO expanded by a factor of 2.8 times, but the concentration of ECO remained the same as it was at 2.8ATA.

This was supported by the data from the CO offgassing, which took into account RMV. The differences between the RMV breathing HBO and air, and HBO and NBO were highly significant, and in proportion to the difference in ambient pressure. Surprisingly, a statistically significant increase in RMV was noted when NBO was breathed compared with air. This may have resulted from the equipment, and the patient subconsciously increasing their rate or depth of breathing, due to anxiety, or slightly increased respiratory effort to trigger the inspiratory valve. It is apparent from the above data, that HBO does not increase the ECO concentration, but it causes increased excretion of CO by mass action of greater gas density. This results in increased minute volume when this is depressurised to one atmosphere.

Matched pair calculations of ECO/COHb demonstrated consistently higher ratios than the values determined by regression line gradients. The most likely explanation for this is the greater influence of extreme values using this method. The regression line uses a "least squares" calculation that reduces the influence of the extreme values

Mathieu et al (1999) reported their findings (in abstract only), the relationship between end-tidal CO and COHb. A significant linear relationship was found between end-tidal CO and COHb for 79 patients. They found that COHb (%) = 0.12 x ECO ppm (Mathieu et al 1999). Air breathing produced a gradient of 8.33. This increased to 11.1 when patients were treated in HBO. Hence the only other reference to the relationship between *end-tidal CO* and COHb in the literature showed only a small difference between the air and HBO regression line slope. The absolute values of Mathieu's regression slopes were greater than those found in my research. This may have resulted from true *end-tidal* samples being collected by Mathieu's group, as opposed to this thesis that has measured *mean* ECO measurements. End-tidal values would be higher than mean values. It is also possible that Mathieu's COHb sample times were better matched in time to the breath samples, reducing the impact of delays with continuing loss of CO due to ongoing oxygen treatment. Mathieu's group did not report RMV for their population, and did not comment on the y intercepts for their relationship between ECO and COHb. The y intercept is particularly relevant if zero ECO is used as a treatment endpoint, and also important if ECO proves to be a more sensitive indicator of CO body stores than COHb.

When compared with COHb, the observed increase in CO excretion breathing HBO in my study was greater than the findings of Mathieu et al (1999) and colleagues. They noted only a 33% increase in the slope of the end-tidal CO vs COHb curve in HBO compared with air for poisoned patients. It is likely that time delays after COHb sampling, and ongoing removal of CO during treatment, led to lower than expected ECO readings relative to the COHb value, for the poisoned patients.

In this chapter, measurements of ECO were not strictly independent of each other in a statistical sense, because they were taken sequentially, and each reading is likely to have influenced the following reading. For example, breathing NBO may have reduced the CO load prior to the HBO sample. Other than instantaneous single breath sampling, there is no easy way to avoid this effect on the results, in poisoned patients who are being actively treated.

When evaluating ECO versus COHb linear regression slopes, the "y" intercepts were higher for NBO and HBO than when breathing air. Both the slope and the position of the regression line were elevated when breathing higher P_IO_2. This confirmed that greater amounts of CO were excreted in the breath at for the same COHb value. The second group of samples from poisoned patients demonstrated

significantly positive y intercepts for ECO values breathing NBO and HBO, when the COHb was unrecordable. These data suggest that it may be possible to continue to excrete CO from the body by breathing oxygen when the COHb was undetectable by the biochemical method. The data provide support for the use of CO offgassing as a treatment endpoint, because when breathing oxygen, the ECO zero endpoint occurs later than that suggested by COHb measurements.

Expired CO and COHb values measured just before HBO treatment were significantly lower than those obtained in the ED. This reflects significant delays in moving from the ED for HBO.

10.5. Conclusions

The data presented suggest that there is a linear relationship between ECO and COHb for poisoned individuals, when breathing air, NBO and HBO. The results need to be interpreted cautiously because of the small sample size in the poisoned group. Overall, the data suggested that for a given COHb, elevating the P_IO_2 caused the ECO, and hence CO elimination to increase. There was no significant difference in the ECO in HBO at 2.8ATA, compared with NBO, however HBO caused a significant increase in the *volume* of CO excreted after it was depressurised to 1ATA. For all samples, the ECO versus COHb regression line showed positive values for ECO, at the point at which COHb was unrecordable. Expired CO (breathing oxygen and HBO) was significantly positive, when COHb became unrecordable. This suggests that a poisoned individual may have significant body stores of CO, at the time COHb may be unrecordable. It also suggests that a longer period of oxygen treatment may be required to reduce ECO to zero, than would occur if COHb were the marker of acute poisoning. The data indicate that measurement of ECO may potentially be more useful than COHb as a marker of treatment endpoint, because of greater sensitivity. Measurement of ECO also has advantages over COHb in that it is a non-invasive test.

11. CLINICAL USE OF EXPIRED CO TO DIAGNOSE CO POISONING

Introduction

Carbon Monoxide poisoning has a non-specific clinical presentation. In up to one third of presentations, the diagnosis may be missed in the ED (Barret et al 1985). Measurement of COHb requires an invasive procedure (blood sampling), which may be poorly tolerated by children. Carboxyhaemoglobin taken at the time of poisoning has proven unreliable as a marker of long-term outcome in CO poisoning. Severe CNS toxicity due to CO may be manifest, even when levels of COHb are low. Measurement of ECO is a non-invasive test and it is easily performed in the ED, sampling from a quietly breathing individual. The method is suited to the paediatric population, where it is desirable to keep invasive tests to a minimum in this population. In children, CO poisoning resembles many other conditions including gastroenteritis (Crocker and Walker 1985). In chapters 9 and 10, it was demonstrated that there is a linear relationship between ECO and COHb, but that ECO measurements appear to be more sensitive. Expired CO could still be detected in the poisoned patient breathing oxygen when COHb was unrecordable.

11.1. Aims

The aim of this chapter was to evaluate the use of ECO measurement to diagnose acute CO poisoning in the ED and to correlate ECO with MMSE scores, to determine if ECO was useful in identifying impaired cognitive function consistent with moderate to severe poisoning.

11.2. Methods

The offgassing apparatus was set up as previously described, and used for collecting breath samples from acutely poisoned patients (less than 6 hours previous) presenting to the Fremantle Hospital ED. These patients had received only pre hospital care. Subjects were included if they had history consistent with exposure to CO. Subjects were excluded if they had received 100% oxygen treatment in a hospital setting for their CO poisoning, because this may have substantially altered their CO breath reading. Because of the potential confounding influence of smoking in the poisoned population, the group was analysed both as a whole, then separately for smokers and non-smokers. The CO readings for poisoned patients were then compared with the control populations of non-poisoned smokers and nonsmokers.

The ECO measurements for non-smoker controls and smoker controls were recruited from volunteers who had attended a quit-smoking stand at the Rockingham-Kwinana Health Expo, described in chapter 7.

In the second part of this chapter, the acute ECO and COHb were correlated with MMSE scores. The MMSE is a validated test of cognitive function impairment (Folstein et al 1975), and has been also used to assess cognitive function in acutely CO poisoned patients (Scheinkestel et al 1999). When used to assess a CO poisoned patient, MMSE $\leq$ 25 was regarded as a sign of severe CO toxicity (Scheinkestel et al 1999).

11.3. Results

11.3.1. ECO as a diagnostic test for CO poisoning

Of the 12 patients with acute poisoning; there were 11 males and one female (mean age 34.7 years, 95% CI = 28.8 to 40.5). It was not possible to select a sample of poisoned patients with equal numbers of males and females, because of the large numbers of males attempting suicide in the population. These patients were described in chapters 9 and 10. They constituted a subset of all poisoned patients who presented during the prospective study of ECO in poisoned patients.

A comparison of the demographics of the poisoned population, smoker controls, and non-smokers is shown in table 11.1. Nine of the CO poisonings were smokers, and three were non-smokers. All were exposed to CO in suicide attempts. Their mean COHb level was 16.3% (95% CI 9.5 to 23.2), and their mean ECO (air) was 66.2 ppm (95% CI = 30.5 to 101.9). Data was not collected on the number of cigarettes smoked per day in the poisoned patients. Smoker controls smoked a mean of 15.7 cigarettes per day (95% CI = 13.9 to 17.6).

Table 11.2 shows a comparison of ECO measurements in nonsmokers and smoker controls, and acutely poisoned patients, and the statistical analysis of the comparison.

Table 11.1. Demographics of the poisoned and control populations:

Control Population	Number	Mean Age (95% CI)	Age Range	Number of Females	Number of males
(A) Non-smoker	**80**	32.8 (29.9-36.6)	13 to 74 years	44	36
(B) Smoker Controls	**119**	26.57 (23.8-29.3)	9 to 75 years	57	62
Acutely Poisoned Sample	**12**	34.67 (28.8-40.5)	19 to 59 years	1	11

Table 11.2. Comparison of ECO measurements in non-smokers and smoker controls, and acutely poisoned patients:

Control Population	Number	Mean COHb (%) (95%CI)	Mean ECO(ppm) (95% CI)	Comparison between mean ECO levels	P value
(A) Non-smoker	**80**	0.06 (0.0 to 0.2)	1.8 (1.5 to 2.1)	Nonsmoker - Poisoned Difference between means = -64.4 ± 6.1	P < 0.0001
(B) Smoker Controls	**119**	2.8 (1.8 to 3.9)	15.9 (14.1- 17.8)	Nonsmoker - Smoker Difference between means = -14.1 ± 1.2	P < 0.0001
Acutely Poisoned Sample	**12**	16.3 (9.5 to 23.2)	66.2 (30.5-101.9)	Smoker - Poisoned Difference between means = -50.2 ± 5.8	P < 0.0001

Using an unpaired two-tailed t test, the ECO for poisoned patients compared with smokers was significantly different. The acutely poisoned patients also had significantly greater ECO values compared with the control non-smokers. The control smoker population was also significantly different from the control non-smoker population ECO.

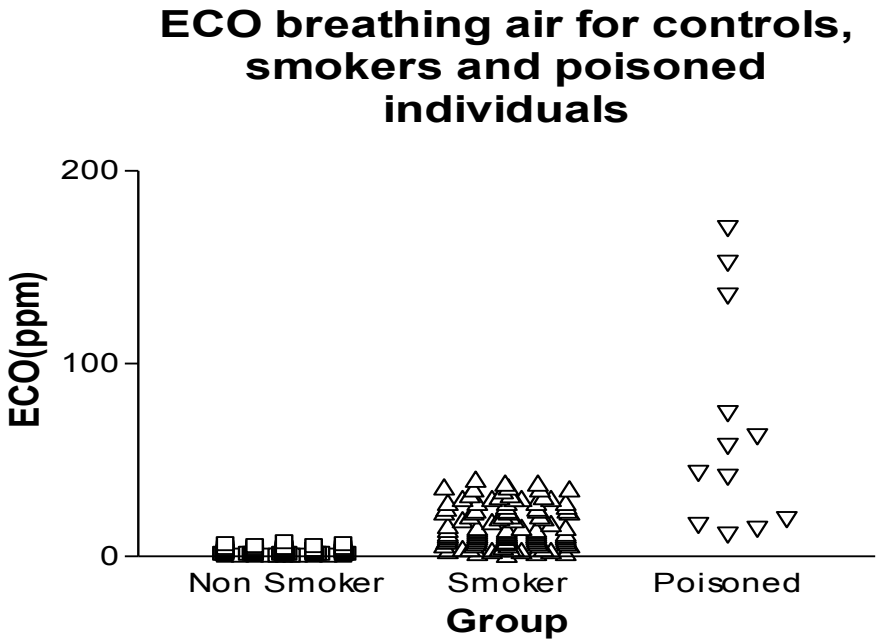
Because of the potential for smoking to act as a confounder in the poisoned group, this group was split into smokers and nonsmokers, for analysis. No significant difference was noted in ECO levels for poisoned smokers versus poisoned non-smokers in this sample, although numbers were extremely small with 9 smokers and 3 non-smokers.

Expired CO values for the poisoned individuals were compared with the non-smoker and smoker controls. These provided similar results to the combined poisoned sample comparisons, being significantly different from the controls: This is summarised in table 11.3, and figure 11.1 demonstrates the data graphically.

Table 11.3. ECO measurements comparing smoker and non-smoker controls with smoker and non-smoker poisoned patients:

Control Population	Number	Median ECO (Range)	Comparison between median ECO levels	P value
(A) Non-smoker controls	**80**	1.0 (0 - 7)	Non smoker vs Smoker Mann-Whitney U = 254.5	P < 0.0001
(B) Smoker controls	**119**	12.0 (1 - 40)	Smoker vs Poisoned Mann-Whitney U = 210.0	P < 0.0001
(C) Acutely poisoned	**12**	50.0 (11 - 170)	Non smoker vs Poisoned Mann-Whitney U = 0.00	P < 0.0001

Figure 11.1. ECO measurements for the poisoned smoker and non-smoker groups, and controls:



An ECO measurement > 40 ppm was selected as a diagnostic level for acute poisoning, because all individuals who were not poisoned had ECO readings of 40 ppm or less. All non-poisoned individuals

who had ECO readings between 7 ppm and 40 ppm were smokers. Using the ECO level of 40 ppm, sensitivity, specificity, positive and negative predictive values were calculated. These are summarised in Table 11.4.

Table 11.4. Use of ECO > 40 ppm to predict poisoning in individuals exposed to CO < 6 hours previously

	Poisoned	Not Poisoned	Total	
ECO > 40 ppm	8	0	8	Positive Predictive Value = 1.0
ECO ≤ 40 ppm	4	199	203	Negative Predictive Value = 0.98
Total	12	199	211	
	Sensitivity = 0.67	Specificity = 1.0		

A further calculation was undertaken using ECO level > 10 ppm, which included the lowest value observed for poisoned patients (table 11.5).

Table 11.5. Use of ECO > 10 ppm to predict poisoning in individuals exposed to CO < 6 hours previously

	Poisoned	Not Poisoned	Total	
ECO > 10 ppm	12	74	86	Positive Predictive Value = 0.14
ECO ≤ 10 ppm	0	125	125	Negative Predictive Value = 1.0
Total	12	199	211	
	Sensitivity = 1.0	Specificity = 0.63		

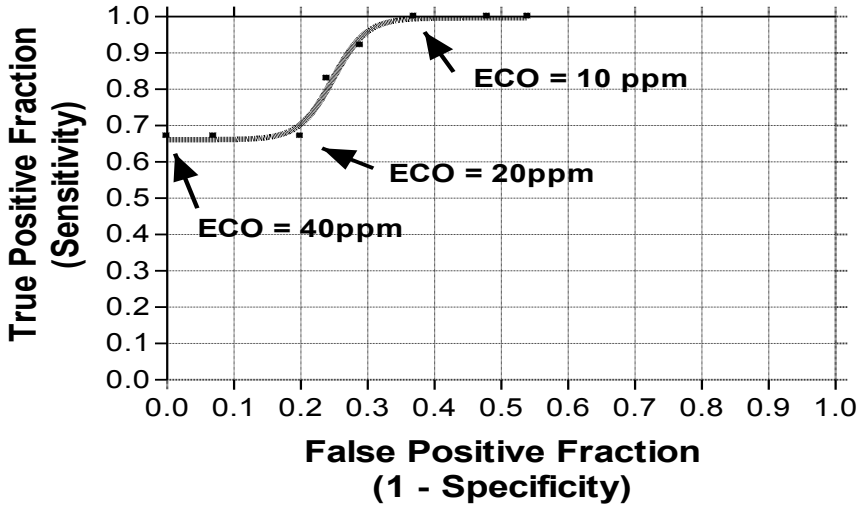
Sensitivity, specificity, positive predictive value and negative predictive value were calculated for a range of ECO values to assess the usefulness of the test in diagnosing CO poisoning in the above population. The results are shown in table 11.6.

Table 11.6. Calculations of sensitivity and specificity, positive predictive value and negative predictive value for the diagnosis of acute CO poisoning across a range of ECO values:

ECO Value (ppm)	**Sensitivity** (True positive fraction)	**Specificity**	**1 – Specificity** (True negative fraction)	**Positive Predictive Value**	**Negative predictive value**
> 5	1.0	0.46	0.54	0.10	1.0
> 7	1.0	0.52	0.48	0.11	1.0
> 10	1.0	0.63	0.37	0.14	1.0
> 12	0.92	0.71	0.29	0.16	0.99
> 15	0.83	0.76	0.24	0.18	0.99
> 20	0.67	0.80	0.20	0.17	0.98
> 25	0.67	0.87	0.13	0.24	0.98
> 30	0.67	0.93	0.07	0.38	0.98
> 35	0.67	0.97	0.03	0.62	0.98
> 40	0.67	1.0	0.0	1.0	0.98

A receiver operating characteristic (ROC) curve was plotted for ECO as a diagnostic test of acute CO poisoning. The area under the curve was 0.92 (figure 11.2). The curve has an unusual shape created by the fact that there is no improvement in sensitivity in the range between 40 ppm and 20ppm. This may be influenced by ECO values in smokers ranging up to 40ppm, and the fact that the group of poisoned patients had all been exposed up to 6 hours previously.

Figure 11.2. Receiver operating characteristic curve for ECO as a diagnostic test of acute CO poisoning:



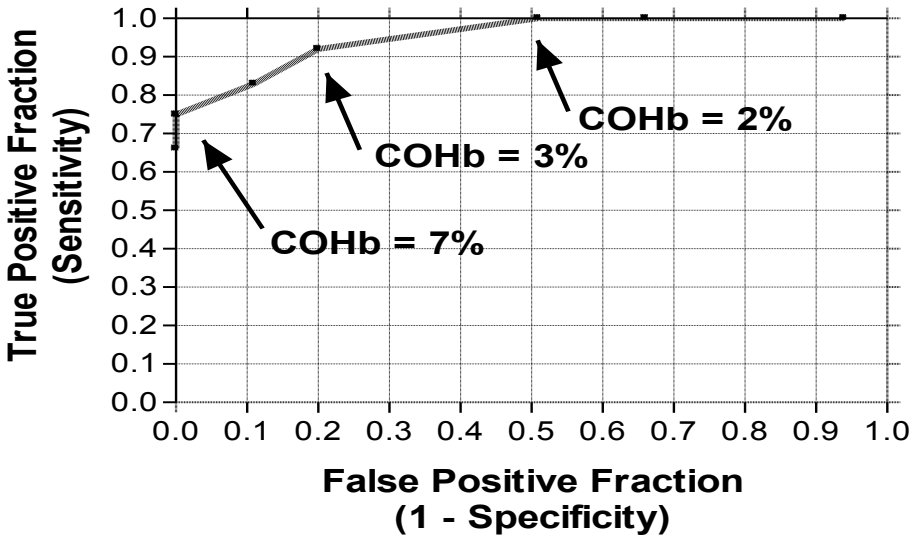
Of the above population, 23 non-smoker controls, 40 smoker controls agreed to provide blood samples for COHb measurements (refer to tables 9.1 to 9.3). In addition to the acutely poisoned patients, these samples were used to calculate sensitivity, specificity, positive predictive value and negative predictive value for a range of COHb values to assess the usefulness of the test in diagnosing CO poisoning, and compare it with ECO values. The results are shown in table 11.7.

Table 11.7. Calculations of sensitivity and specificity, positive predictive value and negative predictive value for the diagnosis of acute CO poisoning across a range of COHb values:

COHb Value (%)	Sensitivity (True positive fraction)	Specificity	1 – Specificity (True negative fraction)	Positive Predictive Value	Negative predictive value
>1	1.0	0.48	0.52	0.27	1.0
>2	1.0	0.67	0.33	0.36	1.0
>3	0.92	0.76	0.24	0.42	0.98
>4	0.92	0.90	0.10	0.65	0.98
>5	0.83	0.94	0.06	0.71	0.97
>6	0.75	0.98	0.02	0.90	0.95
>7	0.67	1.0	0.0	1.0	0.94
>10	0.67	1.0	0.0	1.0	0.94

A receiver operating characteristic (ROC) curve was plotted for COHb as a diagnostic test of acute CO poisoning (figure 11.3). This demonstrated an area under the curve of 0.95.

Figure 11.3. Receiver operating characteristic curve for ECO as a diagnostic test of acute CO poisoning:



11.3.2. Correlation of ECO and COHb with MMSE scores in individuals exposed to CO up to 6 hours previously

Acute MMSE scores measured in the ED were available for all except two of the 12 poisoned patients. Two patients were comatose and unable to cooperate. A score of zero was allocated to these patients. The following table shows the MMSE compared with the acute ECO and COHb levels

Table 11.8 ECO, COHb and MMSE for the 12 acutely poisoned patients in individuals exposed to CO < 6 hours previously

Sex	Age	ECO Air (ppm)	COHb (%)	MMSE
m	38	11	2.5	29
m	26	14	5.5	30
m	44	19	4.8	29
m	42	26	7.0	28
m	48	41	15.0	20
m	41	43	17.0	24
m	41	57	15.0	23
f	19	62	18.0	22
m	24	74	16.0	20
m	29	135	27.0	23
m	36	152	36.0	0
m	27	170	32.0	0

An ECO > 40 ppm predicted a MMSE ≤ 25 in poisoned patients with the following sensitivity, specificity, positive and negative predictive values.

Table 11.9 Relationship between MMSE and ECO in diagnosis of CO Poisoning for individuals exposed to CO < 6 hours previous:

Parameter	MMSE ≤ 25 (Severely Poisoned)	MMSE > 25 Less severely poisoned)	Total	
ECO > 40 ppm	8	0	8	Positive Predictive Value = 1.0
ECO ≤ 40 ppm	0	4	4	Negative Predictive Value = 1.0
Total	8	4	12	
	Sensitivity = 1.0	Specificity = 1.0		

The ability of the COHb level to predict MMSE ≤ 25 was calculated for the same patients using a value of COHb > 25% to define severe poisoning (Scheinkestel et al 1999, Weaver et al 2002). This resulted in low sensitivity and negative predictive value (table 11.10).

Table 11.10 Comparison of MMSE with COHb > 25% in diagnosis of CO Poisoning

Parameter	MMSE ≤ 25 (Severely Poisoned)	MMSE > 25 Less severely poisoned)	Total	
COHb > 25%	3	0	3	Positive Predictive Value = 1.0
COHb ≤ 25%	5	4	9	Negative Predictive Value = 0.44
Total	8	4	12	
	Sensitivity = 0.38	Specificity = 1.0		

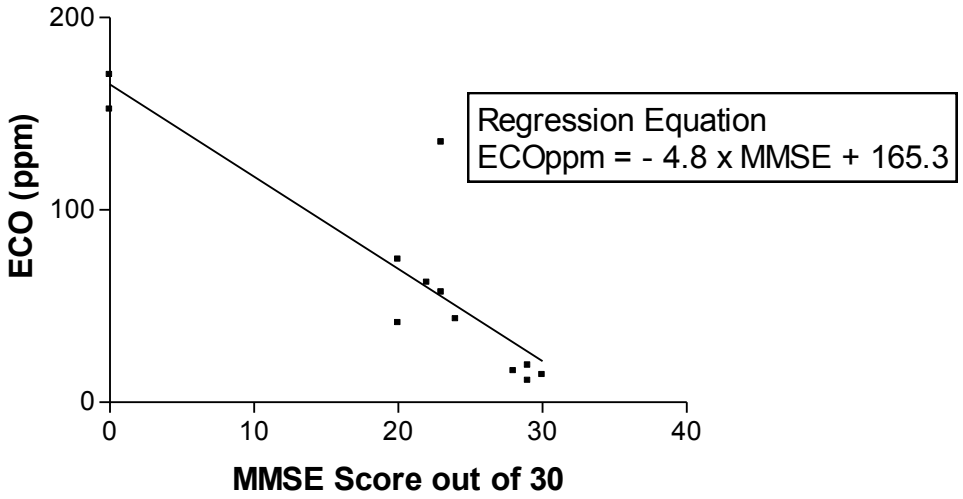
When a level of COHb = 15% was chosen as a critical value, the test was more consistent with choosing a critical ECO value of 40 ppm (table 11.11)

Table11.11 Comparison of MMSE with COHb > 15% in diagnosis of CO Poisoning

Parameter	MMSE ≤ 25 (Severely Poisoned)	MMSE > 25 Less severely poisoned)	Total	
COHb ≥ 15%	8	0	8	Positive Predictive Value = 1.0
COHb < 15%	0	4	4	Negative Predictive Value = 1.0
Total	8	4	12	
	Sensitivity = 1.0	Specificity = 1.0		

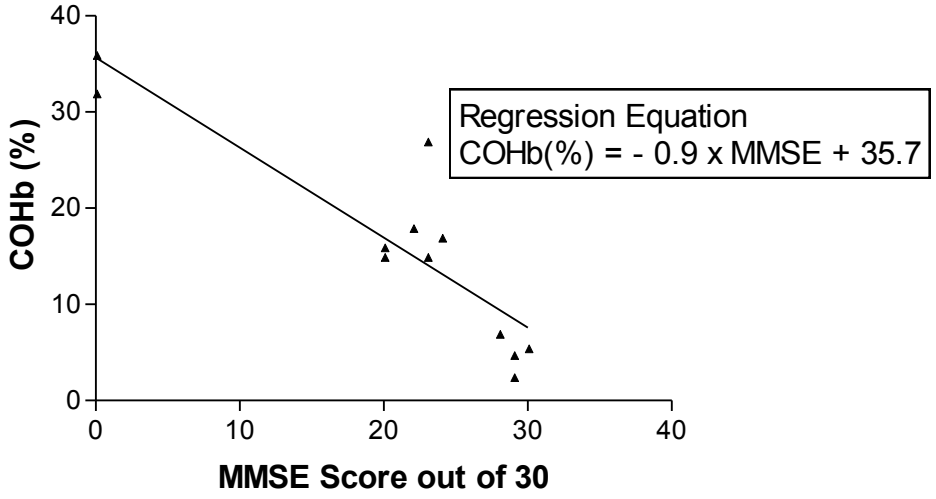
The correlations between MMSE, ECO and COHb are shown in figures 11.4 and 11.5. The regression slope for ECO versus MMSE score was -4.8 (95% CI -6.7 to -2.9) with $r^2 = 0.77$, $p = 0.0002$. This was a highly significant negative correlation was observed

Figure 11.4. Graph showing correlation of ECO with MMSE measured in ED for acutely poisoned patients



The regression slope for COHb versus MMSE score was - 0.9 (95% CI -1.3 to -0.6) with $r^2 = 0.80$, $p = 0.0001$. This was a highly significant negative correlation.

Figure 11.5. Graph showing correlation of COHb with MMSE measured in ED for acutely poisoned patients



11.4. Discussion

In this chapter of the study, measurement of ECO was used to attempt to separate the acutely poisoned patient from others (non-smokers and smoker controls). To ensure that they were truly acute cases, the poisoned patients selected had been exposed to CO less than 6 hours prior to presentation, and received only prehospital care (ie they had not received any definitive treatment for their CO poisoning apart from prehospital oxygen).

Expired CO measurements demonstrated that poisoned patients could be distinguished from the control populations. Similar results were obtained when the poisoned population was divided into smokers and non-smokers.

From a clinical viewpoint however, the specificity and sensitivity of measuring ECO is relevant. If ECO is used as a diagnostic test in the ED, then it must be able to distinguish the individual patient who is poisoned by CO from a heavy smoker. Above a value of 40 ppm, the CO offgassing was 100% specific - ie there were no false positives, and from this population, the test is able to identify all poisoned patients. Unfortunately, this specificity was at the expense of the ability to pick up true positives (sensitivity). For ECO readings greater than 40 ppm, the sensitivity was 0.67. This meant that there would be four false negatives out of 12 poisoned patients, at ECO > 40 ppm. In this population, using a selected value of 40 ppm, clinical information was still required to differentiate these four poisoned patients from smokers. Sensitivity was improved to 1.0, and negative predictive value 1.0, if the selected ECO value was > 10 ppm CO. This was at the expense of specificity, and positive predictive value. Hence there is a range from 10 ppm to 40 ppm where clinical information would be required to diagnose CO poisoning. In practice, it is usually not difficult to obtain this information if one suspects CO poisoning, and the patient's clinical condition is consistent with CO poisoning. All of the four patients with ECO values < 40 ppm were conscious when assessed in the ED and had MMSE Scores of 28 - 30; hence a history was available. This was confirmed when plotting the ROC curve. The ROC curve had an area under the curve of 0.92 that indicates that measuring ECO may be a useful test to diagnose of CO poisoning. However, the ROC curve was an unusual shape with no improvement in sensitivity between 40 and 20ppm ECO. This may have been influenced by ECO values in smokers ranging up to 40ppm. It clearly limits the value of the test for the diagnosis of CO poisoning in this range. Clinically it is probably better to over diagnose a problem, so that poisoned cases will not be missed. The lowest ECO value that would ensure no poisoned cases were missed is 10 ppm. However

in the above data, this would cause 37% of individuals (smokers) to receive treatment when they were not poisoned. Hence ECO requires additional clinical information to be useful as a diagnostic test in the range of 10ppm to 40ppm.

The sensitivity of the ECO test may have been affected by time delays to attend and measure breath samples. Some delays in this study occurred because call-in time for the author or assistants. During this time, the poisoned individuals had received hospital treatment with 100% oxygen, which is likely to have reduced their ECO levels. If used as a screening test, ECO measurements could be taken soon after arrival and initial stabilisation of the patient, if a history of CO poisoning was not forthcoming in a cognitively impaired patient. In these circumstances, a value > 40 ppm would diagnose CO poisoning, a value of ≤ 7 ppm would rule it out with certainty (provided they had been poisoned less than 6 hours previously), and a value of 8 - 40 ppm would require questioning about possible CO exposure, and smoking habit. This is consistent with data from Cunnington and Hormbrey (2002) who found that ECO > 6 ppm suggested exposure to an exogenous source of CO.

Expired CO has similar performance to COHb as a diagnostic test for CO poisoning. Measurement of COHb is the current "gold standard" for the diagnosis of CO poisoning. In this study, the area under the ROC curve for COHb was 0.95. At a value of 7%, COHb was 100% specific for the diagnosis of CO poisoning, and it had a positive predictive value of 1.0. At this value COHb sensitivity was 0.67, which was identical to the sensitivity of ECO > 40 ppm. From this data it can be concluded that ECO and COHb are equivalent in their applicability for diagnosing acute CO poisoning. This was expected, given the significant linear relationship between ECO and COHb, determined in previous chapters. Both tests have limitations for the diagnosis of CO poisoning (COHb in the range of 2 – 7%, and ECO in the range of 8 – 40 ppm), most likely as a result of the overlap of smokers in these ranges. They also require the CO poisoning to be acute < 6 hours previously. Additional clinical information is therefore required in these ranges.

Mini-mental state examination scores of 25 or lower are reported as indicating cognitive deficits are present (Folstein et al 1975). The choice of ECO > 40 ppm as an indicator of acute CO poisoning is validated in this small sample of acutely poisoned patients. In this small sample, the value of 40 ppm enabled differentiation of the group with more significant acute CO toxicity with a sensitivity of 1.0, and specificity of 1.0 in predicting cognitive deficits. Researchers have used COHb levels of >25% to define significant CO poisoning (Scheinkestel et al 1999, Weaver et al 2002). In this small sample,

using COHb levels > 25% to predict cognitive function deficit, there were a significant number of false negatives using the COHb. The lack of correlation between COHb and the cognitive status of the patient was covered in detail in the literature review. My data from the small sample of patients studied, is consistent with the findings of others (Norkool and Kirkpatrick 1985,Gorman et al 1992, Myers and Thom 1995). The ECO value of 40 ppm was a more effective predictor of acute neurological status of the patient, than the quoted literature COHb value of 25%. However, if a lower level, COHb = 15% was chosen for the critical value defining *severe* CO poisoning, then COHb was equal in accuracy to ECO. A more appropriate value for the COHb may be 15% to define severe acute poisoning, provided the poisoning was less than 6 hours prior to sampling. I am unaware of any studies correlating ECO or COHb with acute cognitive impairment in the ED.

More work is needed in this area with a larger sample of poisoned patients. Mathieu and coworkers studied 79 patients, and quoted an end-tidal value of 50 ppm to diagnose CO poisoning with an accuracy of 91%. End-tidal values would be expected to be higher than mean ECO, because the mean is attenuated by dead space air that contains only CO from the environment. They did not however report a control group and hence there were no figures for the sensitivity, specificity or ROC curves for the test (Mathieu et al 1999). Mathieu's group also did not relate their end-tidal CO value to the MMSE. A strongly negative correlation was observed in my study for both ECO and COHb when compared to MMSE in acutely poisoned patients in the ED.

11.5. Conclusions

In acute CO toxicity, ECO and COHb measurements have been shown to correlate negatively with cognitive function (measured by MMSE in the ED). Expired CO and COHb proved equally efficacious in identifying acutely poisoned individuals, with certain limitations. Critical values of ECO >40 ppm or COHb > 7% were shown to be highly specific for CO poisoning, provided the poisoning had taken place less than 6 hours previously. Expired CO levels greater than 40 ppm were 100% specific and 100% sensitive in identifying severe CO poisoning with acute cognitive impairment. Above 7 ppm, the ECO test was highly sensitive in identifying individuals who had been exposed to an external source of CO (smoking or poisoning). In the range of ECO = 8 – 40 ppm, clinical information is required to separate the less severely poisoned patient from the smoker, however this should be possible, because all poisoned individuals with ECO <40 ppm were able to cooperate with cognitive testing. Due to small numbers in the sample, the ECO measurement was not correlated with other indicators of severe CO poisoning such as loss of consciousness, however the two most severely affected patients (initially comatose) had the highest ECO readings. Expired CO > 40ppm and COHb ≥ 15% had equal sensitivity and specificity in discriminating between severely poisoned and less severely poisoned patients.

12. FACTORS AFFECTING CO LOAD, ECO AND CLINICAL CONSEQUENCES OF CO POISONING

Introduction

CO is usually taken into the body and excreted via the lungs. Known exceptions are methylene chloride poisoning (absorbed through the skin then metabolised to CO), and some experimental situations where CO was added to haemoglobin in vitro, or was injected intraperitoneally.

When inhaled, CO is rapidly absorbed into the blood, because its affinity for haemoglobin is 220 to 240 times that of oxygen. Carbon monoxide load may be influenced by the CO concentration in the inspired gas, the duration of exposure, and the RMV of ventilation of the subject (Routley 1998). In this chapter, the factors affecting body CO load in a prospective case series were examined.

12.1. Aim

The aim of this chapter was to examine factors that may influence CO load and ECO in poisoned individuals.

12.2. Methods

All patients eligible for entry into the prospective clinical trial were studied in this chapter. The population consisted of all patients referred for treatment of acute CO poisoning at Fremantle Hospital from April 1992 to September 1993. Patients were prospectively allocated to treatment groups using the protocol that was outlined in chapter 8, table 8.1. Factors that may have influenced CO load at the time of poisoning were compared to ECO measured at entry to the study.

A number of factors were considered likely to influence the CO load. These factors could potentially influence clinical outcomes. It was expected that higher CO load at the time of poisoning would lead to higher ECO levels in the individuals studied.

The following factors were analysed in the study population:

(I) The duration of exposure – this was recorded if available. Longer exposure duration was expected to increase CO load.

(II) The intent of exposure – stratified into accidental versus deliberate self-harm. Deliberate exposures were expected to increase CO load.

(III) The source of CO – leaded and unleaded petrol, industrial or other sources. Leaded petrol was expected to produce higher CO levels than unleaded petrol.

(IV) The delay to initial oxygen treatment (hours) and delay to study entry (hours). Delays to study entry were expected to reduce the measured level of CO, due to offgassing.

(V) Neurological status on arrival in the ED. It was expected that higher CO load would cause greater neurological impairment.

Expired CO breathing air and oxygen, and COHb were assessed to determine if significant relationships existed with any of the above factors

Patients received a neurological rank based on the degree of impairment when they arrived in the ED. These ranks were a surrogate indicator of CO load and severity of poisoning. Expired CO was correlated with the neurological ranks summarized in table 12.1.

Table 12.1 - Neurological ranks on arrival in the ED

Neurological Rank Score	Definition
1	Coma (GCS ≤ 8)
2	Neurologically impaired (GCS = 9-13)
3	Cognition Impaired (GCS ≥ 14 and MMSE ≤ 25)
4	Normal (GCS = 15 and MMSE ≥ 26).

12.3. Results

Sixty-six patients were considered for this chapter of the study. All 66 provided data for the time to 100% oxygen treatment, and all 66 had times measured to study entry (intention to treat). Three patients refused to enter the study, and one patient was a referral with DNS three weeks after his poisoning. Two other patients had greater than 48 hours before referral for HBO treatment, and had unrecordable CO in their breath. These patients had severe neurological injury, were receiving intensive care life support, and later died. Sixty patients had ECO measurements breathing 100% oxygen at study entry.

On arrival at the Fremantle Hospital ED, ECO were measured for the population of 60 patients. The mean ECO breathing air was 15.5 ppm (95% CI = 5.9 to 25.1). The mean ECO breathing oxygen was 37.7 ppm (95% CI = 21.1 to 54.4). The mean COHb was 11.2% (95% CI = 8.2 to 14.2)

12.3.1. Duration of exposure to CO, and source of CO

The mean duration of exposure for the whole poisoned population (n=66) was 3.9 hours (95% CI = 2.8 to 5.0 hours). The group with deliberate exposure to CO (n=40 analysed) had a mean exposure of 3.9 hours (95% CI = 2.4 to 5.4 hours), compared with accidental exposure (21 analysed) 4.0 hours (95% CI = 2.4 to 5.5 hours), p=0.94.

Individuals who lost consciousness had significantly longer exposures than those who didn't. Mean exposure duration for the group with LOC was 4.9 hours ± 0.9 (37 analysed), compared with 2.5 hours ± 0.5 (23 analysed) for those remaining conscious. This difference in exposure duration was significant: -2.4 hours (95% CI = - 4.6 to -0.2 hours), p = 0.03. The relationship between ECO breathing air and duration of exposure to CO was not statistically significant ($r^2 = 0.003$, p = 0.7).

There was no significant difference between COHb levels measured for patients who had LOC (11.8% ± 1.8) versus no LOC (9.1% ± 2.5), p = 0.41. There was no significant difference in ECO levels breathing air for individuals with LOC (21.9ppm ± 11.1) versus no LOC (12.9ppm ± 4.5), p=0.37. There was no significant difference in ECO levels breathing oxygen for individuals with LOC (36.9ppm ± 9.9) versus no LOC (38.5ppm ± 16.0), p=0.93.

12.3.2. Intent of exposure – suicidal versus accidental

Table 12.2 summarises acute ECO levels breathing air and oxygen, and COHb levels for suicidal individuals compared with accidental poisoning. All values were significantly higher in the suicidal population.

Table 12.2 Comparison of suicidal versus accidental exposures: ECO breathing air and oxygen, and COHb

	ECO breathing air (ppm)		ECO breathing oxygen (ppm)		COHb (percent)	
	Suicidal	Other	Suicidal	Other	Suicidal	Other
Mean ± SD	23.3 ± 7.1	2.5 ± 0.5	47.8 ± 11.4	9.2 ± 2.1	14.2 ± 2.0	4.9 ± 1.5
Difference between means	20.8 ± 9.5		38.6 ± 11.6		9.3 ± 2.5	
p value	0.03		0.002		0.0004	

Individuals whose exposure to CO was part of a suicide attempt were more likely to lose consciousness compared with those who had accidental exposure, p = 0.004, Fisher's exact test (summarised in table 12.3). The relative risk of LOC for those attempting suicide = 2.21 (95% CI = 1.17 to 4.20)

Table 12.3 Deliberate or accidental exposure to CO and loss of consciousness

Origin of CO	Loss of Consciousness ?	
	Yes	No
Suicide	31	13
Accidental/Other	7	15

12.3.3. Source of CO and ECO

Individuals who exposed themselves deliberately to CO in acts of self harm were more likely to use automobiles as a source of CO 41/44 versus 4/22, $p < 0.0001$, Fisher's exact test, (table 12.4). Leaded petrol exhaust was more likely to be the source of CO in the individuals with deliberate exposure, than with accidental exposure, 27/44 versus 3/22 $p = 0.0002$.

Table 12.4 Source of CO versus exposure intent

Source of CO	Exposure Intent	
	Accidental	Deliberate
Leaded petrol	3	27
Unleaded Petrol	1	14
Indoor BBQ	15	0
Unknown/Other	3	3

There was no significantly increased risk of losing consciousness for the group poisoned by leaded petrol compared with other sources of CO ($p= 0.08$, leaded petrol versus other). This is shown in table 12.5.

Table 12.5 Source of CO and loss of consciousness

Source of CO	Loss of Consciousness ?	
	Yes	No
Leaded petrol	21	9
Unleaded Petrol	8	7
Indoor BBQ	6	9
Unknown/Other	3	3

Significantly higher ECO values breathing air or oxygen were noted for individuals poisoned by CO from leaded petrol exhaust when compared to those poisoned from other sources (table 12.6). The COHb levels were not significantly different.

Table 12.6 Comparison of ECO breathing air and oxygen, and COHb levels for leaded petrol source of CO versus other CO source

	ECO breathing air (ppm)		ECO breathing oxygen (ppm)		COHb (percent)	
	Leaded Petrol	Other	Leaded Petrol	Other	Leaded Petrol	Other
Mean ± SD	32.8 ± 11.8	7.5 ± 3.9	71.4 ± 20.4	23.2 ± 7.2	14.1 ± 2.0	9.8 ± 2.0
Difference between means	25.3 ± 9.8		48.3 ± 17.2		4.3 ± 3.2	
p value	0.01		0.007		0.19	

The subgroup of individuals with deliberate exposure (n=43 with full data for analysis) was split by source of CO into leaded petrol exhaust (n=27) versus unleaded exhaust and other (n=16). There was no significant difference in neurological scores in the ED for those exposed to leaded petrol, compared with unleaded. No significant difference was detected in this subset for the entry features age, exposure time, or initial COHb. Expired CO levels were significantly higher for those exposed to leaded petrol exhaust, compared with unleaded, when breathing NBO, and the difference was not quite significant when breathing air (summarised in table 12.8).

Table 12.8 Individuals with deliberate self-harm – split by source of CO (Leaded petrol versus unleaded petrol exhaust)

	Patients with deliberate self-harm subset		
Entry Feature	**Leaded Petrol exhaust Mean (95% CI)**	**Unleaded Petrol Exhaust Mean (95% CI)**	**Analysis**
Age (years)	Mean = 28.4 years (24.7 to 32.2)	Mean = 31.6 years (25.8 to 37.5)	Difference between means = -3.18 ± 3.18, t=1.00 df=41, p = 0.32
Exposure Duration (hours)	Mean = 4.5 hours (2.1 to 6.8)	Mean = 2.8 hours (1.4 to 4.2)	Difference between means = 1.61 ± 1.55 hours, t=1.04 df=38, p = 0.30
Neurological rank in ED	Mean = 2.4 (2.1 to 2.8)	Mean = 2.9 (2.5 to 3.4)	Mann-Whitney U = 158.0, p = 0.15
Initial COHb	Mean 15.4% (10.8 to 20.0)	Mean = 13.5% (7.4 to 19.5)	Difference between means = 1.9± 4.1, t=0.64 df=41, p = 0.64
Initial ECO breathing air	Mean = 39.1 ppm (9.9 to 68.4)	Mean = 11.1 ppm (0 to 25.0)	Difference between means = 28.0 ± 13.9, t= 2.01 df = 35, p = 0.05
Initial ECO breathing NBO	Mean = 83.4 ppm (34.2 to 132.5)	Mean = 32.6 ppm (8.2 to 57.0)	Difference between means = 50.8 ± 23.5, t=2.16 df=40, p = 0.04

12.3.4. ECO correlated with delay to initial oxygen treatment and study entry

There was no significant relationship observed between delay to study entry and ECO breathing air or NBO. No significant relationship between delay to study entry and COHb was observed. There was no significant relationship between delay to oxygen treatment and the ECO breathing air or NBO. A negative correlation was observed between delay to oxygen treatment and the initial COHb measured in the ED (slope = - 0.34 ± 0.15 % COHb per hour, 95%CI = -0.63 to –0.04, y intercept = 13.0 ± 1.6, 95% CI = 9.7 to 16.3). These results are summarised in table 12.7.

Table 12.7 Table showing delays to study entry and NBO treatment correlated with ECO and COHb

		R^2 value	P value
Delay to study entry vs	ECO breathing air	0.03	0.23
	ECO breathing NBO	0.04	0.12
	COHb	0.02	0.23
Delay to NBO treatment vs	ECO breathing air	0.02	0.24
	ECO breathing NBO	0.03	0.18
	COHb	0.08	0.03

Mean delay from initial assessment to study entry for 60 patients with available data was 12.2 hours (SD 13.4, 95% CI = 8.7 to 15.6 hours). The mean delay from commencing 100% oxygen treatment to HBO treatment at Fremantle Hospital was 8.7 hours (95% CI = 6.3 to 11.1 hours).

The difference in the time from initial assessment, to study entry for the two treatment groups, HBO and 100% oxygen, was significant. Mean time to study entry was 13.9 ± 2.0 hours (n=47) for the group allocated to hyperbaric oxygen treatment, and 5.8 ± 2.6 hours (n=13) for the 100% oxygen group (p = 0.05). The difference between means = 8.1 ± 4.1 hours. The delay to study entry for patients allocated HBO treatment was due to the need to transfer more severely poisoned individuals to Fremantle Hospital Hyperbaric facility. These delays reduced the mean amount of CO measured in the breath at study entry. Delays also occurred at Fremantle Hospital – the fall in ECO measurements comparing the ED samples (mean = 66.2ppm) and hyperbaric samples (mean = 8.8 ppm) was demonstrated in chapter 10.

The HBO treated group included 18 patients for whom there was a delay of more than 12 hours before treatment with HBO. Two patients from separate incidents took more than 48 hours from their time of (self) extrication to the time they received 100% oxygen. These individuals were confused and wandering through bush when found by searchers. Three other patients had long prehospital transfers via the Royal Flying Doctor service, from remote areas of Western Australia. They received high flow oxygen during transfer. All five above were cases of deliberate self-harm, and the individuals delayed their definitive treatment, by seeking to avoid detection. If the five prolonged delays were excluded from analysis, then the mean delay to 100% oxygen for the 55 other patients was 2.8 hours, (95% CI = 2.0 to 3.6).

12.3.5. Neurological rank at entry correlated with ECO and COHb

There was a significant correlation noted between the severity of poisoning measured by neurological impairment, and the ECO breathing air ($p = 0.005$, slope = -15.1, 95% CI = -25.5 to – 4.8) and NBO ($p= 0.002$, slope = -26.9, 95% CI = -43.3 to – 10.4), figures 12.1 and 12.2. The correlation between neurological rank (table 12.1) and COHb was also significant ($p = 0.71$, slope = -5.3, (95% CI = -8.1 to –2.4), figure 12.3.

Figure 12.1 ED neurological ranks compared with ECO breathing air

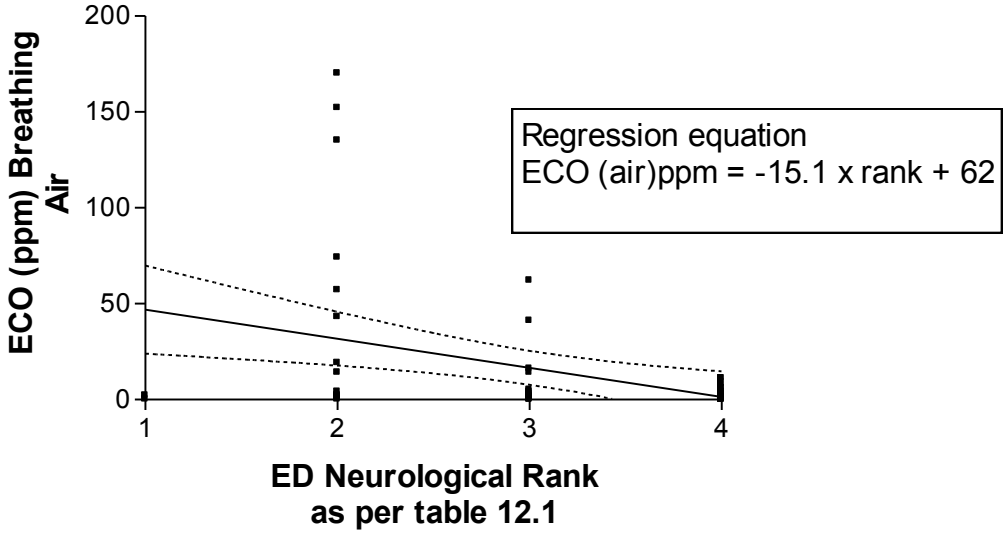


Figure 12.2 ED neurological ranks compared with ECO breathing NBO

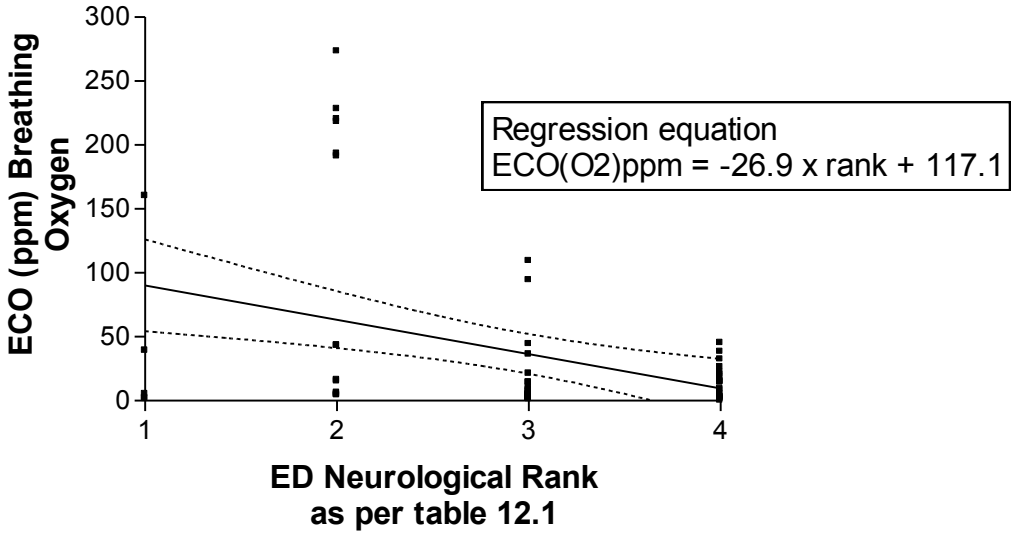
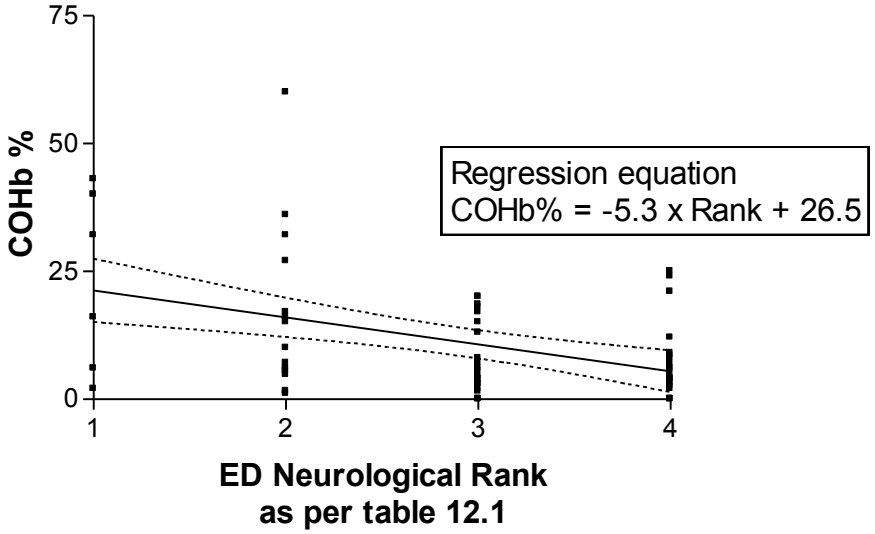


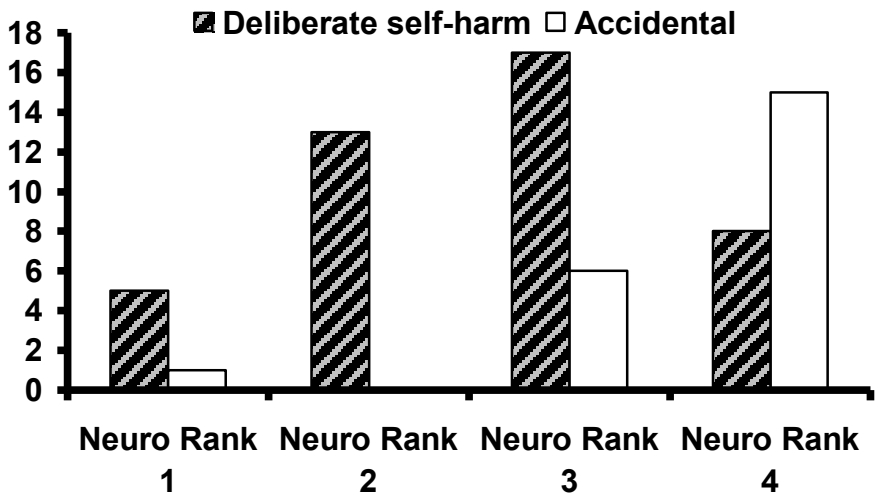
Figure 12.3 ED neurological ranks compared with COHb



ED neurological status for deliberate versus accidental exposure

When ranked according to neurological status on arrival in the ED, individuals with deliberate CO exposure (n=43 analysed) were more neurologically impaired, compared with those suffering accidental CO poisoning (22 analysed). The mean neurological rank for those with deliberate CO exposure was 2.6 (95% CI = 2.3 to 2.9), and mean rank for accidental CO exposure was 3.6 (95% CI = 3.3 to 3.9), Mann-Whitney U = 199.0, p=0.0001. These results are shown in figure 12.4.

Figure 12.4 ED Neurological ranks - deliberate versus accidental CO exposure for 65 patients where data was known



Individuals with deliberate exposure to CO consumed alcohol or other drugs in 24/44 cases, compared to 0/22 case who had accidental exposure, $p < 0.0001$ Fisher's exact test.

12.4. Discussion

In this series, no significant difference in duration of exposure to CO was observed when comparing those with deliberate self-harm and with those exposed to CO accidentally. Individuals who had LOC were exposed significantly longer than those who remained conscious. This was expected, because once consciousness was lost they were "trapped" in the CO environment. Despite the longer exposures, there was no significant difference in ECO, or COHb levels for individuals with LOC versus those with no LOC. Duration of exposure data relied on self-reporting, or observer reports, and was potentially inaccurate or at best, an estimate. Expired CO data were also affected by time and type of treatment received before initial samples were obtained. Individuals with LOC may have been more likely to receive supplemental oxygen, which would have reduced their ECO.

A significant difference in clinical severity of poisoning was noted for suicidal individuals with deliberate self-harm, compared to those with accidental exposures. Individuals with deliberate exposure to CO were more likely to use automobiles for their source of CO, and were more likely to use leaded petrol source. Suicidal individuals were more likely to experience LOC, and were clinically more severely poisoned on arrival in the ED. Suicidal individuals also had higher ECO values and COHb levels than the group with accidental poisoning. This probably reflects their intent at the time of exposure. The main contributing factors in the greater degree of poisoning for suicidal individuals, was exposure to leaded petrol exhaust, and their concomitant use of drugs and alcohol. Measurements of ECO from individuals exposed to leaded petrol exhaust were higher than those exposed to other sources. This difference held even for the suicidal subset. COHb levels were also higher in individuals exposed to leaded petrol exhaust. Leaded petrol exhaust is known to contain significantly higher CO levels than unleaded petrol exhaust, due to catalytic converters used in the latter engines (Routley 1998). Most accidental CO exposures were to sources other than motor vehicle exhaust, and there usually was an attempt to escape from the environment, once symptoms were noticed. The suicidal group also had a high rate of co-ingestion and alcohol consumption; factors independent of CO, potentially exacerbating their neurological toxicity, and risk of impaired consciousness. Further correlation of entry factors with respect to outcome occurs in chapter 15. The intent of deliberate self-harm in this study population, led to more serious exposures with greater toxicity than the population sustaining accidental exposure.

Delays to treatment and study entry did not significantly correlate with ECO levels, and delay to study entry did not significantly correlate with COHb levels. However there was a significant negative correlation with the delay to NBO treatment and the COHb – longer delays led to lower COHb levels. In general, it was expected that longer delays would result in lower ECO and COHb, however these would have been influenced by variability in oxygen dose provided to poisoned individuals prior to study entry. Carbon monoxide is removed from the body at different rates when breathing air or oxygen (see chapter 13). It was not possible to collect pre-study oxygen treatment data accurately.

A negative correlation was found between ECO breathing air and oxygen, COHb, and the neurological rank of the patient in the ED. Higher levels of ECO and COHb correlated significantly with a lower (worse) neurological rank. This was an expected finding, as it is known that CO is toxic to the CNS. Most studies have attempted unsuccessfully to correlate COHb with neurological outcome *after* treatment (Norkool and Kirkpatrick 1985, Myers et al 1985, Fang et al 1986, Gorman et al 1992). In these studies, the sampling time of COHb was not recorded, and the acute effects of CO were not documented. Damage to the CNS results from both toxic and anoxic effects of CO. It would be expected that the initial injury from CO would correlate with the degree of acute poisoning, however, some of the CNS damage may not be reversible, creating difficulties in correlating initial CO load with final outcomes. Individuals with deliberate CO exposure were more neurologically impaired, compared with those suffering accidental CO poisoning. This was an expected finding, given their increased risk of LOC and the use of leaded petrol exhaust as a source of CO.

12.5. Conclusions

It has been demonstrated in this case series of 66 patients, individuals with LOC had longer exposures to the CO source than those without LOC, but did not have significantly higher ECO or COHb levels. Individuals with deliberate exposures had higher COHb and ECO levels than accidental exposures, and had worse neurological ranks when assessed in the ED. This provided evidence that both ECO and COHb are suitable markers of acute toxicity. Deliberate exposures to CO resulted in greater neurological toxicity and were more likely to cause LOC, than accidental exposures. The greater toxic effect in deliberate exposures was most likely due to greater use of automobiles with leaded petrol (and hence higher CO) and possible co-ingestions (covered in chapter 15). There was however, no significant difference in exposure duration when comparing deliberate versus accidental exposures. Delays to treatment and study entry did not significantly affect ECO levels, however there was a significant negative correlation between initial COHb and the delay to NBO treatment. In general, ECO and COHb measurements had a similar relationship to acute neurological CO toxicity, and higher levels of ECO and COHb positively correlated with more severe poisoning.

13. ELIMINATION KINETICS USING ECO

Measurement of ECO as the final pathway for excretion was investigated in this chapter of the project.

13.1. Aims

The aims of this chapter of the study were as follows:

(1) To determine the elimination kinetics of CO using ECO measurements in poisoned subjects and to compare these with the elimination of CO from haemoglobin

(2) To examine in detail ECO elimination kinetics in poisoned subjects, including the influence of age, comparisons between males and females, smokers and non-smokers, and compare with elimination of CO from Hb.

13.2. Methods

Description of cases for the measurement of expired CO and COHb elimination

Patients with ECO > 10 ppm in the prospective series of poisoned patients were investigated in this part of the study. Carbon monoxide elimination kinetics were assessed while patients underwent NBO and/or HBO treatment. All patients received ECO measurements in real-time, as described in chapter 8.

Regardless of treatment, acutely poisoned patients had their ECO measured until zero level was reached. Two indices of CO elimination were recorded:

(1) Rate of elimination of CO over time, and

(2) Time to reach zero CO in the breath.

Times were recorded from study entry to reaching zero ECO. This zero CO reading was the limit of the apparatus in detecting CO, (less than one part per million).

Once entered into the study, ECO levels and RMV were tabulated during treatment (5 minutely during HBO and 10 minutely during NBO), until zero was reached. Curves were produced for the concentration of ECO (ppm) versus time, and elimination rate of CO (ml/minute) versus time. Both elimination indices were calculated, because of the potential variability of RMV, and the potential differences in RMV for the different treatment regimens. Comparisons were made for treatment in NBO and HBO. Because the sample consisted of poisoned patients referred for treatment, no measurements were made breathing air.

Comparisons of "goodness of fit" were made by the curve-fitting program Graphpad Prism®, version 2.0 (Graphpad Software Inc, San Diego California USA). The elimination kinetics of CO were determined by comparing "goodness of fit" of two models, single phase exponential or two phase exponential. These models were chosen, based on work of previous authors, as the most likely to appropriately fit the CO elimination data.

The data for each patient were analysed using each of the models. Comparisons were then made between these models. Analysis of the most appropriate curve within each mathematical model took place by the least sum of squares method using the Graphpad Prism® computer program. Parameters in the equation were progressively changed until the sum of squares was reduced to its minimum.

Graphpad Prism® produced a graph that minimised the sum of the squares of the vertical distances of the data points from the curve. This was determined to be the "best fit" for the model. The two mathematical models were then compared for each set of data to determine which model best described the data.

A single half-life (if appropriate) was calculated if the model was determined to be first order exponential elimination. If a two-phase exponential model was determined to best fit the data, then two separate half-lives were calculated. In circumstances where the comparison of the above data was indeterminate, other mathematical models such as a hyperbolic curve were tested. Elimination curves for each allocated treatment (HBO or NBO) were dealt with separately.

13.2.1. Two-point method for calculation of COHb elimination

Carboxyhaemoglobin levels were taken before and after a standard treatment for individuals in the hyperbaric treated group, and before and during treatment in the NBO treated group. Samples were restricted to two points, (two to seven hours apart) because of limited access to the patient within the hyperbaric chamber, and practical issues regarding some overnight sampling in NBO treated patients. It was recognised from the outset that this would cause limitations in interpreting the data. To calculate the elimination kinetics of CO from haemoglobin, assumptions were required, based on the more precise kinetics determined from the CO offgassing. Previous authors had shown that an exponential model was valid, so a general method for calculating COHb half-life was followed, using an exponential equation for elimination kinetics (Peterson and Stewart 1970). A two-point method was followed for calculation of COHb half-life. It was not possible to calculate half-lives by the two point method when the post treatment reading was zero. This would have led to seeking the natural logarithm of zero in the exponential equation, which could not be mathematically defined. The method is outlined below:

Mathematical derivation of the two-point method for COHb half-life calculation

For a single-phase exponential elimination process, the concentration, C_1 is an exponential function of the original concentration, C_0.

$C_1 = C_0.e^{-kt}$ Where C_0 is the initial COHb, and C_1 is the COHb after exit from the treatment, t is time, and k is the rate constant of elimination of CO

Hence $C_1/C_0 = e^{-kt}$

Hence $\text{Ln}\,(C_0 / C_1) = kt$

Therefore $k = \text{Ln}\,(C_0 / C_1) / t$

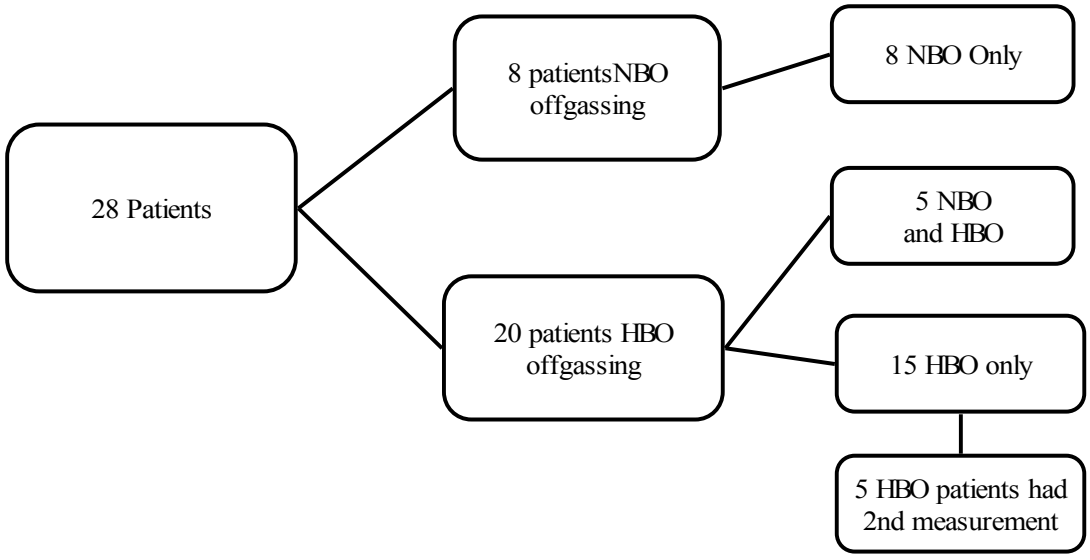
Once k is known, then the half-life can be calculated, because after one half-life, $C_0/C_1 = 2$. The following formula applies:

$T_{½} = \text{Ln}(2)/ k$ **Therefore** **$T_{½} = 0.693/ k$**

13.3. Results

Detailed measurement of CO elimination was undertaken in 28 patients who had breath CO levels greater than 10 ppm. A total of 13 patients had detailed CO offgassing measurements taken during NBO treatment. Eight of these received NBO as their only treatment, and the other five received HBO treatment after initial NBO CO offgassing measurements. Twenty patients had detailed CO offgassing measurements during HBO treatments. Five of these had sufficient data from NBO to calculate both HBO and NBO half-lives. Hence, a total of eight patients contributed solely NBO data, fifteen contributed HBO data, and five contributed both HBO and NBO CO elimination data this is summarised in figure 13.1

Figure 13.1 Summary of origin of patient data for chapter 13.



Data were available to calculate elimination curves from 20 patients treated with HBO and 13 during treatment with NBO. Five patients had CO offgassing measured during two HBO treatments, hence data was available from 25 HBO treatments. Of 38 readings taken, 14 had starting ECO ≥ 10 ppm and 24 had starting ECO ≥ 20 ppm.

Another 35 patients had breath CO studied until ECO reached zero, however detailed study of their CO elimination did not occur for a number of reasons. Three patients with ECO readings of greater than 10 ppm missed detailed CO offgassing measurements. Many patients had significantly reduced ECO levels when they arrived at Fremantle Hospital, due to delays in transfer for HBO treatment (described in chapter 14). Thirty-two had breath CO readings of less than 10 ppm, and 25 had readings

of ≤ 5 ppm, when they arrived at Fremantle Hospital breathing 100% oxygen. These ECO values were considered too low for reliable calculation of elimination kinetics, because they were in the range of non-smoker controls (chapter 9).

For all but three of the HBO treatments, there were two elimination curves available; one showing fall in CO concentration (ppm), and the other showing a fall in the rate of CO offgassing (mL/minute) (total = 47 curves). There were 24 curves available from the 13 patients receiving 100% oxygen. The curves are located in appendix 18.6.

13.3.1. ECO Elimination Curves – best fit mathematical model

Of the 47 curves analysed during hyperbaric oxygen treatments, The Graphpad Prism ® program determined the best fit to be a single-stage exponential decay model in 46. This confirmed that it was appropriate to use a single-stage exponential model and half-lives to describe elimination of CO from the body. Similar results were obtained for elimination of CO using NBO, where 23 out of 24 curves had "best fit" equations consistent with single-stage exponential kinetics.

13.3.2. Calculated elimination half-lives using ECO and CO Offgassing

Two methods were used to calculate the elimination half-lives of CO:

(1) The progressive reduction in the ECO in parts per million (ppm), [ppm method]

(2) Calculation of CO offgassing (in mL/min), taking into account the subject's RMV [mL/min method].

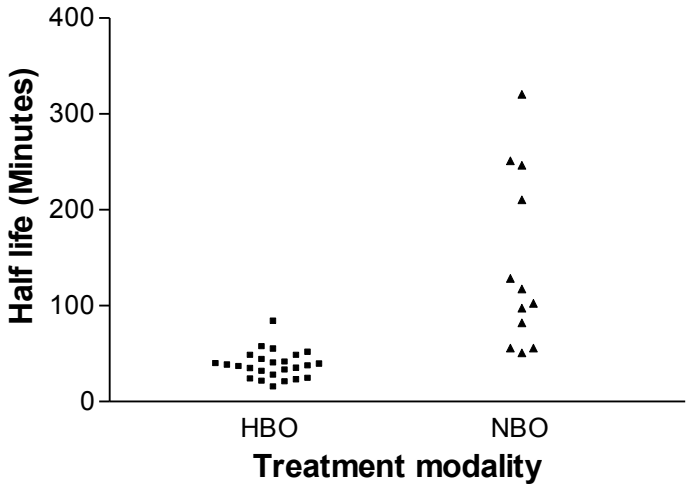
The half-lives derived from the data are summarised in table 13.1.

Table 13.1 Calculated elimination half-lives in NBO and HBO

Record No.	Sex	Smoking Status	Age	$T_{1/2}$ HBO ppm (minutes)	$T_{1/2}$ HBO mL/min (minutes)	$T_{1/2}$ NBO ppm (minutes)	$T_{1/2}$ NBO mL/min (minutes)
A034	M	Smoker	44	20.0	7.7		
B072	M	Smoker	24	34.3	21.3		
C024	M	Smoker	29	36.4	34.0		
C717	M	Non-smoker	23	56.6	46.1		
C726	M	Smoker	30	38.7	35.5		
D042	M	Smoker	30	38.6	23.1	211.7	
D423	M	Smoker	25	33.7	34.6		
D423	M	Smoker #2		26.8			
D428	M	Smoker	26	50.7	35.7		
D428	M	Smoker #2		22.7	57.9		
D712	M	Smoker	41	22.1	31.8	57.3	58.7
E024	M	Non-smoker	48	39.5	42.2		
E050	M	Smoker	41	30.8	49.0	52.2	80.3
E200	M	Smoker	36	32.3	46.3		
G073	M	Smoker	28	40.7	40.1		
G425	M	Smoker	42	37.5	61.5		
G714	F	Non-smoker	19			129.8	112.7
H072	M	Non-smoker	41	54.3		103.9	103.8
J056	M	Non-smoker	38			247.8	65.0
J723	M	Smoker	27	35.7	27.5		
J723	M	Smoker #2		83.0			
K069	M	Non-smoker	30			321.8	266.4
K217	M	Smoker	38	23.6	22.1		
K217	M	Smoker #2		47.6	23.5		
K613	F	Smoker	22	20.4	12.6		
L432	M	Non-smoker	26	14.5	42.1		
L432	M	Nonsmoker#2		47.4	55.0		
E727	M	Smoker	30	43.1	52.4		180.0
A070	M	Non-smoker	26			57.1	46.7
D314	F	Non-smoker	40			98.9	68.7
H040	F	Smoker	27			118.8	118.8
K220	M	Non-smoker	46			252.4	136.5
L220	M	Non-smoker	40			83.4	83.4
MEAN			**32.8**	**37.2**	**36.5**	**144.6**	**110.1**
SD			**8.2**	**2.9**	**3.0**	**26.2**	**17.9**
95% CI			**29.6 to 35.9**	**31.2 to 43.3**	**30.0 to 42.9**	**86.9 to 202.2**	**70.8 to 149.4**

There was no significant difference between the half-lives during HBO treatment calculated using the ppm method versus the mL/min method, p= 0.86. There was also no significant difference between the half-lives during NBO treatment using the two methods, p=0.29. The difference in half-lives was highly significant when comparing NBO with HBO treatment, using each of the calculation methods. Using fall in CO concentration offgassing [ppm method], the difference between the means was 107.4 minutes ± 18.4, $p < 0.0001$. Using the fall in excreted volume of CO [ml/minute method], the difference between the means was 73.6 minutes ± 13.7, $p < 0.0001$. Hyperbaric oxygen treatment resulted in a significant reduction of elimination half-life. The difference between treatments half-lives for all patients using the CO offgassing is shown graphically in Figure 13.1.

Figure 13.1
Half lives for patients treated with HBO and NBO (mL/minute method)



13.3.3. Factors affecting elimination half-lives

The effect of age, sex and smoking status on CO elimination half-lives was examined.

Effect of age on elimination half-life

From the data in this study, age had no relationship with calculated elimination half-lives, in either HBO or NBO, when calculated by either method.

Differences in elimination half-lives between sexes – NBO Treatment

The data from patients breathing NBO was analysed to determine if there was a difference between male and female half-lives when breathing NBO. There was no significant difference between the elimination half-lives of the three females compared with the nine males (table 13.2) however, low numbers in each group may have affected this result.

Table 13.2 CO elimination half-lives for males and females treated with NBO

	Males (n=9) NBO half-life (mL/min method)	Females (n=3) NBO half-life (mL/min method)	Males (n=9) NBO half-life (ppm method)	Females (n=3) NBO half-life (ppm method)
Mean	113.4	100.1	154.2	115.8
SD	70.9	27.3	104.0	15.7
95%CI	58.9 to 167.9	32.2 to 167.9	74.2 to 234.1	76.9 to 154.8
P value	0.76		0.62	

Differences in elimination half-lives between sexes – HBO treatment

The HBO data is summarised in table 13.3. There was only one female treated with HBO with half-life data, and her measured T ½ was 12. 6 minutes (mL/min method), and 20.4 minutes (ppm method). This prevented any meaningful statistical analysis, so the data in table 13.3 is amalgamated.

Table 13.3 CO elimination half-lives for males and females treated with HBO

	(n = 22) HBO half-life (mL/min method)	(n = 25) HBO half-life (ppm method)
Mean	36.4	37.2
SD	14.5	14.6
95%CI	30.0 to 42.9	31.2 to 43.3

Smoking habit and CO elimination half-life

Because of the significant influence of treatment method on CO elimination half-life, smokers and non-smokers were divided into treatment groups of NBO and HBO, to determine if smoking influenced patients' elimination half-lives. Table 13.4 above summarises the results. No statistically significant difference was noted for smokers CO elimination compared with non-smokers, in NBO or in HBO. Small subgroups may have affected this result.

Table 13.4 Smoking habit and CO elimination half-lives

Half-life calculation	Smoker half-life (minutes)	Non-smoker half-life (minutes)	P value using t test
100% oxygen using ppm method	**110.0 (n=4)** 95% CI = 0 to 228.1 minutes	**161.9 (n=8)** 95% CI = 80.3 to 243.5 minutes	**0.37** t=0.93, df=10
100% oxygen using the mL/min method	**109.5 (n=4)** 95%CI = 24.8 to 194.1 minutes	**110.4 (n=8)** 95% CI = 52.4 to 168.4 minutes	**0.98** t=0.02, df=10
HBO using ppm method	**35.9 (n=20)** 95% CI = 29.3 to 42.6 minutes	**42.4 (n=5)** 95% CI = 21.3 to 63.5 minutes	**0.38** t=0.88, df=23
HBO using the mL/min method	**34.25 (n=18)** 95% CI = 26.8 to 41.7 minutes	**43.4(n=4)** 95% CI = 36.7 to 56.0 minutes	**0.13** t=1.56, df=20

13.3.4. Comparison of ECO elimination half-lives with COHb half-lives

This section compared the ECO with the COHb. It was not possible to calculate the total body CO load from the COHb alone, hence the volume of CO in the body was not known. Each of the ECO (ppm) and COHb measurements was a measurement of concentration of CO at a given time, and the results are therefore comparable. The measurement of CO offgassing (mL/minute) was a dynamic measurement , and not directly comparable to COHb which was a static concentration at the time of sampling. Hence it was more appropriate to choose ECO.

NBO samples
Comparison of ECO elimination half-lives with COHb half-lives

Table 13.5 shows the half-lives breathing NBO, comparing two-point readings of COHb, with the fall in ECO (ppm) over time.

A comparison was undertaken for the samples in table 13.5 breathing NBO. The measured ECO half-lives were compared with COHb half-lives calculated by two-point method. A trend was observed for longer CO elimination half-lives measuring ECO compared to the COHb elimination half-lives. The result was borderline significant: p = 0.05 (unpaired t test).

Table 13.5
Comparisons of elimination half lives of COHb, and ECO elimination, for poisoned subjects breathing NBO

Record No	Sex	COHb Before Oxygen	COHb During oxygen:	Sample Time difference (minutes)	COHb T ½ (minutes)	ECO T ½ (minutes) ppm method
A034	M	18	4.8	150	78.6	
A070*	M	4	1	125	62.5	57.1
B072	M	16	2.8	225	89.4	
D042*	M	27	1.5	420	100.7	211.7
D428	M	18	5.5	135	78.9	
D717*	M	16	0.2	250	39.5	57.3
H072*	M	15	2.2	330	119.0	103.9
K069*	M	3	0.2	360	92.0	266.0
K220*	M	21	4	240	100.3	252.4
L220*	M	3.1	0.5	240	60.7	83.4
E050	M					52.2
H040	F					118.8
G714	F					129.8
D314*	F	4	0.2	240	55.5	98.9
				Mean T ½	**79.7**	**130.1**
				SD	**27.8**	**87.4**
				95% CI	**55.5 to 102.0**	**68.2 to 214.5**

From table 13.5, further analysis of 8 matched samples (marked *) was undertaken. In the 8 matched samples, significantly longer half-lives were observed for ECO elimination compared with the COHb elimination (paired t test, p=0.046, mean of differences = 62.6 minutes, (95% CI = 1.4 to 123.7). Because of low numbers in each group, this result should be interpreted with caution.

HBO Samples
Comparison of ECO elimination half-lives with COHb half-lives

Seven patients had COHb still detectable after they had completed their treatment with HBO oxygen. Three other patients may have had detectable CO, but their samples were missed (J723, K217 and L432 in table 13.1). It was possible to calculate the half-life of their COHb using a two-point method and compare this with the ECO elimination half-life (ppm method). Table 13.6 demonstrates the HBO elimination half-lives of COHb ECO for 7 patients where matched samples were available.

Table 13.6
Comparisons of elimination half-lives of COHb, and ECO, for poisoned subjects breathing HBO at 2.8 ATA

Record No	Sex:	COHb Pre HBO:	COHb Post HBO:	Time difference (minutes)	COHb T1/2 (minutes)	CO Offgas T1/2 (minutes)
A034	M	4.8	0.2	100	21.8	20.0
D423	M	43	11	90	45.7	33.7
D428	M	5.5	1	90	36.8	50.7
E024	M	15	1	90	23.0	39.5
E200	M	12	2	90	34.8	32.3
G425	M	7	1	90	32.1	37.5
H072	M	2.2	0.2	90	26.0	54.3
				Mean	31.5	38.3
				SD	8.5	11.6
				95% C.I.	23.6 to 39.4	27.6 to 49.0

Mean COHb half-life in HBO appeared lower than ECO elimination half-life, however using a paired t test, the difference between COHb half-life and ECO half-life was not significant, $p = 0.23$. The seven matched hyperbaric samples were all males. Again, low numbers may have affected this result.

13.4. Discussion

The data presented confirmed that it was appropriate to use a single-stage exponential model and half lives to describe elimination of CO from the body. The majority of equations were consistent with one-stage exponential kinetics.

The data from this study indicate that the elimination half-life of CO as a function of ECO are longer than the values quoted from previous literature for COHb (Pace et al 1950, Peterson and Stewart 1970). Using a different method that took into account changes in patients' respiratory minute volume, half lives calculated by measuring the falling elimination of CO were not significantly different from the falling concentration method. Calculations of half-life were not made in the air environment, because all subjects in this study were being actively treated with NBO and HBO for CO poisoning. The data from this study measuring CO elimination half-lives using ECO provides the largest series of hyperbaric treated patients so far described. The previous largest series was Myers et al (1987) with 12 patients.

The seven previous studies of CO elimination (all using COHb) were summarised in table 5.1. Only two groups measured the COHb half-life in air, 100% oxygen and in hyperbaric oxygen. (Pace et al 1950, and Peterson and Stewart 1970). Five groups measured multiple COHb levels for half-life calculations (Pace et al 1950, and Peterson and Stewart 1970, Myers et al 1987, Jay and McKindley 1987, Weaver et al 2000). Levasseur et al 1996 used two point calculation methods, on the assumptions of the original work by Pace et al, and Peterson and Stewart. My study has confirmed that single-phase exponential elimination kinetics is appropriate for CO elimination from the lung.

Pace et al (1950) were the first to investigate CO elimination in detail, including the effects of increases of P_IO_2. They calculated elimination half-lives of COHb in 15 healthy subjects, aged between 20 and 40. Table 13.7 summarises their results:

Table 13.7

CO elimination half-lives from Pace et al's data - half-lives quoted in minutes

P_IO_2 (ATA)	Males		Females	
	Number	T ½ (minutes)	Number	T ½ (minutes)
0.2 (air)	5	249	5	179
1.0 (NBO)	10	47	5	36
2.8 (HBO)	5	22	5	15

The values calculated by Pace et al for COHb are lower than my calculations measuring ECO. Confidence intervals were not provided for Pace's data, however female subjects appeared to eliminate CO more rapidly than males. The values for the HBO samples were provided for males, and showed a range of half-lives from 19.1 to 26.5 minutes. Interestingly, when Pace's data has been quoted in the literature, only the male values have been used (Peterson and Stewart 1970, Weaver et al 2000). Weaver et al (2000), with data from 22 females found no difference in elimination half-lives between the sexes.

Peterson and Stewart (1970) determined COHb elimination half lives of 320 minutes for air (39 experiments), 80.3 minutes for 100% oxygen (2 experiments), and 23.3 minutes for hyperbaric oxygen 3 ATA, (2 experiments). The HBO (3 ATA) and NBO half-lives were calculated from two subjects only (4 values). The values were also lower than my ECO data for NBO and HBO (2.8 ATA). Given that the NBO and HBO values were sourced from only two subjects respectively, Peterson and Stewart's data is of limited value. It has however, been referred to by other authors (Dolan 1985).
Myers et al (1987) studied 24 poisoned individuals treated with NBO (12 subjects) and HBO (12 subjects). Using multiple samples, they determined mean COHb elimination half-lives to be 131 ± 133 minutes breathing NBO and 43 ± 22 minutes breathing HBO at 3 ATA.
Levasseur et al (1996) demonstrated no difference in blood CO half-lives for subjects in NBO, regardless of oxygen delivery method or source of CO. They determined blood CO elimination half lives to be 91 ± 38 minutes for fire victims, 87 ± 40 minutes for pure CO intoxication, 92 ± 40 min for mechanically ventilated patients, and 87 ± 37 minutes for spontaneously breathing. Oxygen concentrations were not measured, and "high flow oxygen 12 - 15 L/min" was assumed to be 100% oxygen. Levasseur also concluded: "in practice, prescribing 100% oxygen in spontaneously breathing patients, does not guarantee its delivery to the lungs". Patients in Levasseur's series had blood taken

for analysis 2.9 ± 1.2 times, and elimination of CO was assumed to be first-order exponential, based on the data of Pace et al 1950.

Jay and McKindley used a Gamov bag to deliver HBO (at 1.58 ATA) to smokers, and compared half-lives of COHb breathing 100% oxygen at 1 ATA and at 1.58 ATA (Jay and McKindley 1997). They found an elimination half-life of 71.3 ± 9.9 minutes in 100% oxygen at 1 ATA, and 26.3 ± 3.7 minutes for HBO (1.58 ATA). Most subjects provided samples every 5 minutes for 40 minutes. They found that zero order kinetics described the CO elimination in the majority of cases in 100% oxygen at 1 ATA, but there was a significant shift towards first order exponential elimination in the hyperbaric environment. The latter figure of 26.3 minutes in 1.58 ATA HBO was determined in a Gamov bag, and was from volunteers with very low COHb levels. It was a low half-life, for the stated inspired oxygen partial pressure (P_IO_2) when compared with the results of other authors and the findings of our study, and its validity is questionable. Jay and McKindley's study may have been weakened by the use of smokers with very low COHb levels (1.16 ± 0.28 g/dl), making it subject to the influence of endogenous CO production. Jay and McKindley may also have experienced difficulties in distinguishing a decay curve from a straight line at these low levels of COHb.

This could also be a potential weakness of my study. The elimination curves for expired carbon monoxide are contained in appendix 18.6, and demonstrate that most of my subjects (24/48) had starting ECO values that were greater than 20ppm, which is above the normal range and also above the mean values determined for smokers determined by other authors 16.4 ppm and 17.1 ppm (Cunnington and Hormbrey 2001, Deveci et al 2004). However there were 14 subjects who had starting ECO values < 20ppm. It is possible that these lower values may have affected my results, however multiple samples were taken which demonstrated clear elimination curves, and exponential elimination.

Weaver et al (2000) examined the half-life of COHb for 93 subjects breathing NBO. Their methods used two point calculations to determine CO elimination half-lives for 76 subjects, and more than 2 points for 17 subjects. For the 93 subjects, the half-life was 74 ± 25 minutes, with a range of 26 to 148 minutes. Weaver's group found no differences between males (n=71) and females (n=22), nor NBO delivery method, however the two-point method produced calculated half-life values which were different to those where three or more COHb samples were used, suggesting that two point methodology may be less reliable than multiple sampling. Data from their series showed that the 17 patients with multiple measurement points, had COHb elimination half lives which were significantly

shorter than those measured using the two-point method (Weaver et al 2000). Weaver's group noted that the COHb elimination half-life was not affected by the method of exposure to CO.

In my study, half-lives calculated from ECO and CO offgassing in NBO 144.6 ± 26.2 and 110 ± 17.9 minutes) and HBO (37.2 ± 2.9 and 36.5 ± 3.0 minutes) were longer than those determined for COHb by all other authors except for Myers et al (1987). Quoting mean CO elimination half-lives does not provide a full representation of the data. In the above studies, recorded values for NBO COHb elimination half-lives ranged between from 80 minutes (Petersen and Stewart 1970), 27 to 462 minutes (Myers et al 1987), 39 to 180 minutes (Levasseur 1996), 57 to 110 minutes (Jay and McKindley 1997) and 26 to 148 minutes (Weaver et al 2000). Breathing HBO the values for COHb elimination half-lives are quoted as 14 to 26 minutes (Pace et al 1946), 23.3 minutes (Petersen and Stewart 1970) 4.2 to 86.4 minutes (Myers et al 1987), 21.4 to 33.2 minutes at 1.58 ATA, (Jay and McKindley 1997).

In my series, a wide range of half-lives during NBO and HBO treatment were determined using the ECO methodology. The 2.8 ATA HBO treated group ranged from 7.7 to 83 minutes (a 1072 percent variation), and the NBO group ranged from 46.7 to 321.8 minutes (a 689 percent variation). This **may** have implications for treating CO poisoning using empirical methods. At this point in time, there is no proof that repetitively treating poisoned individuals to unrecordable ECO is beneficial, and the answer can only be determined with a randomized controlled trial. If there were evidence to show that removal of low levels of CO were beneficial, then applying pharmacokinetic principles, it may be expected that acceptable treatment regimens would proceed for greater than 5 half-lives. Hence required treatment times based on the above data would be 39 to 415 minutes for HBO, and 233 to 1609 minutes (3.9 to 26.8 hours) for NBO.

No relationship was demonstrated between age of the individual and the CO elimination half-life in my series. The majority of CO is eliminated via the lungs, and unless there was significant lung disease present in the poisoned individuals, age would be unlikely to influence the elimination process. All individuals entering the prospective case series were fully independent and had no physical restrictions prior to their poisoning.

I found no significant difference in elimination half-lives demonstrated for smokers versus non-smokers in NBO or HBO. Small numbers may have influenced interpretation of results this chapter of

the study, creating very small subgroups. I have been unable to locate references to the effects of smoker status on CO elimination from the body.

My values for COHb half-life in NBO and in HBO at 2.8 ATA were close to the values described by other authors (Pace et al 1950, Peterson and Stewart 1970, Weaver et al 2000). The results from the eight-paired samples breathing NBO demonstrated a significantly shorter elimination half-lives for COHb when compared to those calculated using ECO. In the HBO environment, there was a trend towards shorter half-life in the COHb group, but this was not statistically significant in the small sample of seven matched pairs. The results suggest that CO elimination in the breath (measured by ECO) may take longer to become unrecordable than CO elimination from Hb. The most likely explanation for this is the imprecision of the biochemical test used to measure COHb. According to Katsumata et al (1981), the methodology used to detect COHb has an accuracy of ± 0.4%. This may have produced inaccuracies for the lower readings of COHb. Since the original experimental work was carried out for this thesis, the biochemical test has been replaced by co-oximetry in most hospitals. Co-oximetry is stated to have a higher level of precision than spectrophotometric techniques at low levels of COHb, and may be superior in defining the ECO-COHb relationship (Widdop 2002).

Further validation of the CO breath analysis may also need to use multiple reference methods such as infrared spectroscopy, and gas chromatography (Heinemann et al 1979, Mahoney et al 1993). Improved validity may also result from multiple blood samples when the COHb is at higher levels. It is possible that the breath test for CO has lower or greater precision than biochemical techniques, however this was not specifically investigated in this study.

It is possible that some errors may have occurred in the calculation of the COHb elimination half lives, due to the two point method, and the fact that for the majority of patients, the second COHb value had returned to the normal range. However, at the time of sampling for COHb, ECO values were still falling, indicating that a steady state was not yet reached for the patient breathing oxygen. According to the Coburn-Forster-Kane equation, there would still be CO being removed from COHb, if ECO was still falling (Coburn et al 1965). A lower baseline level in the order of 0.1 to 0.2% COHb would be expected breathing 100% oxygen. Even if the COHb level had reached steady state, and blood samples were taken late, then the calculated two point half-lives would have been shorter. Hence if errors resulted from COHb reaching normal values then the T ½ would have been over estimated. This

still provides some support that the demonstrated difference between ECO T ½ and COHb T ½ was valid.

Carbon monoxide excreted from the lungs could also originate from dissolved CO, and CO bound to other sites, such as myoglobin in addition to that attached to haemoglobin. Bruce et al (2003) have recently developed a model to describe uptake of CO into muscle myoglobin which better explains discrepancies noted with the CFK equation when COHb is noted to reach steady state. There is a small but steady decline of COHb in the 10 to 40 minute period during CO rebreathing, despite endogenous CO production. This decline was noted to be greater in individuals with greater muscle mass (males > females) (Coburn and Mayers 1971, Sokal et al 1984). Bruce et al's 2003 data suggest that the muscle diffusion capacity for CO is less than one-tenth that of the lung. They also demonstrated that the loading of COMb is also much slower than COHb, requiring 83 hours to reach steady state of 42% COMb breathing 1000 ppm F_ICO, compared with less than 200 minutes to reach steady state of 70% COHb. Myoglobin has a lower calculated Haldane CO affinity ratio (25-36) than haemoglobin (218-248), (Bruce et al 2003). However, due to the relativities of muscle mass (20-29kg) compared with circulating red cells (2.5 kg for haematocrit ~ 50%), the amount of CO that can be stored as COMb may be as much as 153% of the quantity attached to Hb (Sokal et al 1984, West 2000, Bruce et al 2003). This has implications for the washout of CO from the body, if there has been sufficient time for myoglobin to be loaded during CO poisoning. Bruce et al's data suggest that the washout profile of CO from Mb is expected to exhibit a very long tail, indicating that low level CO my still be in the process of elimination from Mb, long after the COHb has returned to normal range. If this is the case, the CO being transported from muscle to the lung may result in only minor elevations in COHb, that are not detectable in COHb measurement, however were able to be detected with ECO measurements. The implications of this low level CO excretion in the treatment of CO can only be determined with a larger prospective randomised controlled trial.

13.5. Conclusions

The one-phase exponential model provided the best fit to the data in 98% of the curves from HBO treatment, and 96 percent of the curves from treatment with 100% oxygen. This finding supports the use of half-lives an appropriate method to describe CO elimination. Half-lives calculated by ECO technique were 110.1 and 144.6 minutes in a P_IO_2 of 1.0 ATA, and 37.2 and 36.5 minutes in a P_IO_2 of 2.8 ATA. There was a seven to ten-fold variation of CO elimination between individuals. Age and

smoking status did not appear to influence elimination of CO via the lungs in this sample of poisoned patients. Comparison of elimination half-lives using COHb and ECO in NBO and HBO trended towards a shorter elimination half-life for COHb, and this was significant in the NBO treatment group. This study provides evidence that CO elimination via the lungs may take longer than it takes for COHb to return to normal range. It is possible that ECO detected in the lung may reflect levels of CO attached to haemoglobin that are undetectable using the biochemical assay in this study. Whether or not this makes a difference clinically would need to be tested with a larger prospective randomized controlled trial.

This study did not measure, or take into account the possibility of CO metabolism, chemical binding of CO, or excretion in sweat, urine or faeces. Input and output of CO could not be correlated, as the former was not known. The non-invasive technique of measuring ECO offers the possibility of tailoring of treatment to each individual's unique elimination kinetics.

14. UNRECORDABLE ECO EVALUATED AS A TREATMENT ENDPOINT AND CORRELATION WITH OUTCOMES AT 3 MONTHS USING NEURLOLOGICAL AND COGNITIVE TESTING

Introduction

Over the last two decades, in the absence of a reliable marker of acute CO poisoning, the severity of CO poisoning has been assessed using clinical parameters. These include:

1. Level of consciousness, with emphasis on LOC at any stage.
2. Impairment of cognition
3. Elevation of COHb above "normal ranges" to confirm exposure

In clinical studies published to date, significant emphasis was placed on detection of impaired mentation because this was the only validated test of significant intoxication with CO (Goulon et al 1969, Choi 1983, Myers et al 1985, Dolan et al 1987, Raphael et al 1989, Elkharrat et al 1991, Gorman et al 1992, Mark 1992, Tibbles and Perrotta 1994, Ducasse et al 1995, Gorman 1995, Thom et al 1995, Mathieu et al 1998, Scheinkestel et al 1999, Weaver et al 2002).

Unfortunately, detecting impaired mentation is less specific if other toxins (for example ethanol or sedatives) had been ingested concurrently with the CO poisoning. Co-ingestions also made it difficult to assess acute response to treatment.

In evaluation of long-term outcomes, patient neurological and cognitive status has been regarded as the best indicator of recovery (Myers et al 1985, Gorman and Runciman 1991, Segar and Welch 1994, Tibbles and Perotta 1994, Van Meter et al 1994, Mathieu et al 1998, Weaver et al 2002). Some studies have used return to the patient's occupation as an indicator of functional outcome (Raphael et al 1989). The main difficulty with all studies to date has been lack of an acute marker to determine treatment end-point. There is no universally accepted "gold standard", leading Gorman and Runciman to conclude "administration of hyperbaric O_2 (at either 2 or 3 ATA for one or two hours) on admission to hospital, and repeated either daily or as made necessary by the patient's condition, is the only adequate treatment of CO poisoning yet demonstrated" (Gorman and Runciman 1991).

It was demonstrated in chapters 12 and 13 that ECO may be a useful marker of persisting total body load of CO. Continuous ECO monitoring is non-invasive and able to be measured in all patients with CO poisoning, regardless of the oxygen delivery apparatus. Expired CO measurement was able to detect CO in the breath at very low levels, even when COHb was unrecordable using biochemical methods. It is possible to identify the point at which CO in the breath becomes undetectable. Zero ECO therefore constitutes a potential measurable end-point against which treatment regimens can be titrated.

14.1. Aims

The aims of this chapter were:

(1) To correlate treatment to unrecordable ECO with acute neurological recovery

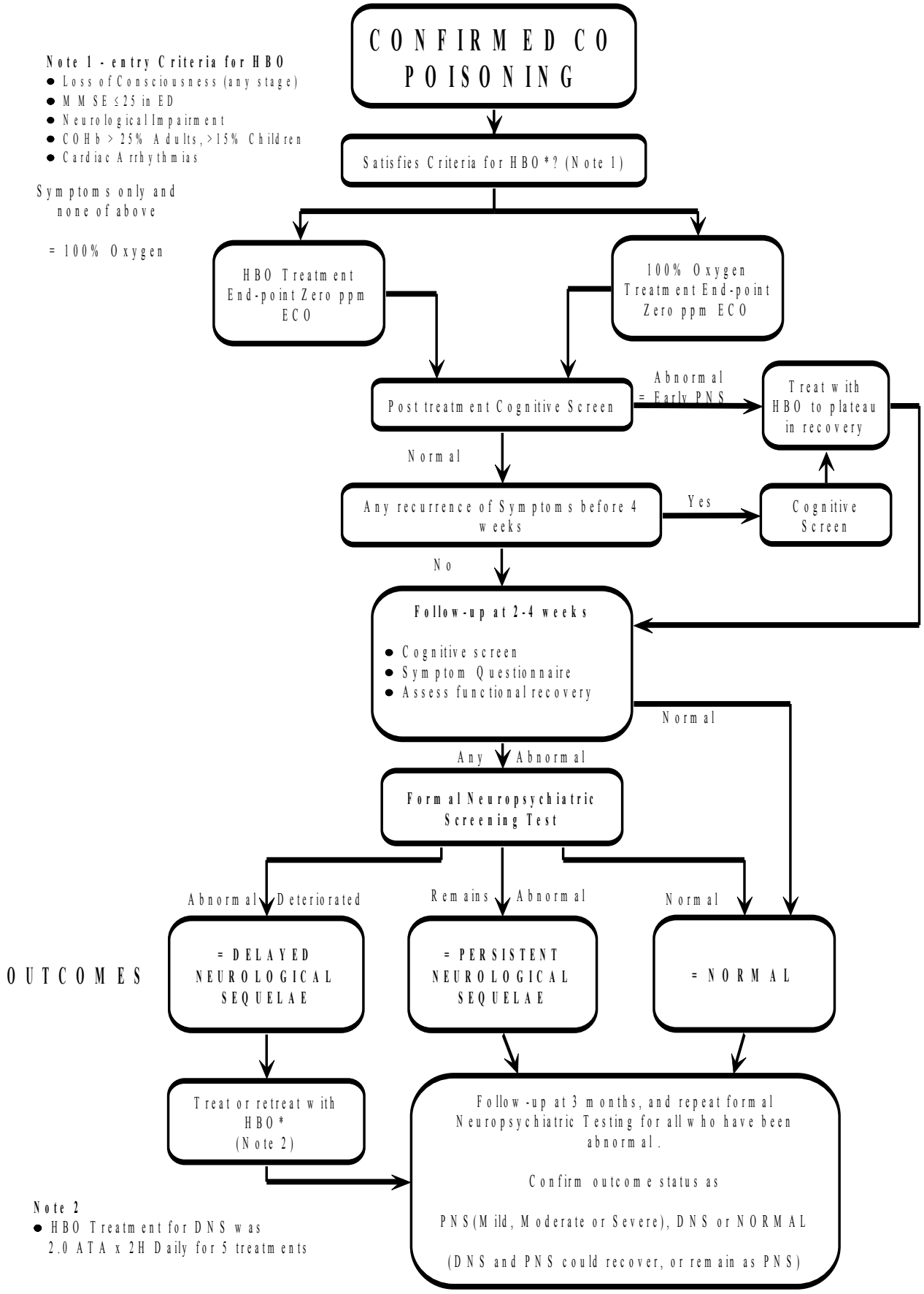
(2) To correlate patient status after treatment to an end-point of zero ECO, with the outcome measures of PNS and DNS, at 3 months

(3) To compare outcomes in this series with those of other authors.

14.2. Methods

The selection of cases, study design and projected numbers, general entry criteria, notification processes, initial assessment, neurological ranking system treatment and ECO methods were described fully in chapter 8. The study flow chart (figure 14.1) is repeated below for clarity. This provides an overview of the methods. Cognitive testing was an essential component of outcome analysis, relating the patient status at the treatment end-point (when ECO was unrecordable) and the final outcome at 3 months. This is summarised in 14.2.1.

Figure 14.1 - Study Flowchart



14.2.1. ED neurological and cognitive testing

Initial neurological and cognitive assessment was carried out in the ED of either Fremantle Hospital or the referring hospital. The MMSE was used as the screening tool for cognitive deficits in all Perth ED's. Patient GCS and MMSE in the ED were recorded at entry to the study, to serve as baseline neurological status from which to assess their response to treatment (appendices 18.2.1 and 18.2.2). Patient neurological status also directed their treatment in accordance with the study protocol (see general entry criteria table 8.1). Patients received a rank based on their neurological status in the ED using the scale in table 14.1 (repeated here for clarity).

Table 14.1 Patient neurological ranks in the ED

Ranking	Definition	Clinical Description
1	Coma	GCS ≤ 8
2	Neurologically impaired	GCS = 9-13
3	Cognition Impaired	GCS ≥ 14 and MMSE ≤ 25
4	Normal	GCS = 15 and MMSE ≥ 26.

After the attainment of unrecordable ECO in the subject's breath, NBO treatment was ceased, and HBO treatment stopped on completion of the planned HBO treatment table. Patients were then subjected to a neurological examination, followed (if they were capable) by cognitive function testing, to evaluate the effects of treatment. This screening included MMSE, timed symbol-digit test (TSDT) (written and verbal), and digit span (DS) recalling digits forward and reverse (appendices 18.2.2, 18.2.3 and 18.2.4). Nurses who had been trained by clinical psychologists administered the tests. The tests were subtests of the Wechsler Adult Intelligence Scale - Revised. (Wechsler 1981), and had also proven useful in the CONSB (Myers et al 1983[1], Meissier et al 1991). Clinical psychologists advised that these tests, combined with the MMSE would be appropriate to screen for deficits known to occur in CO, particularly in the areas of information processing, learning, attention and memory. The cognitive screening tests constituted in effect, four out of six parts of the CONSB validated previously by others (Meissier et al 1991). The results of cognitive screening post treatment (at zero ECO) were recorded for comparison with 3-month outcomes. Abnormal test results were defined as 2 SD below

normal population reference values. Patients with abnormal test scores were further treated with HBO until there was a plateau in their recovery for three successive treatments. If they had scores within normal range, then they were discharged from the hyperbaric medicine unit to be followed up in two to four weeks, or earlier if symptoms consistent with a relapse occurred. Patients and their relatives were given a printed handout outlining the type of symptoms which may occur between treatment and contact details of the investigators, if they or their relatives noted problems.

Follow-up with the Hyperbaric Medicine Unit occurred at two to four weeks. At follow-up, patients were questioned specifically about symptoms that may have been consistent with neuropsychiatric abnormality functional status questionnaire, FSQ, appendix 18.3, and also a general health questionnaire, GHQ-12 appendix 18.4 (Goldberg and Blackwell 1970, Goldberg and Williams 1988). Patients were again administered the cognitive screening tests described above. Any individuals with abnormal screening test scores, persistent significant symptoms, or deteriorating test scores in the first 4 weeks were referred to clinical psychologists for more detailed cognitive function testing (see appendix 18.5). The psychologists knew that patients had received treatment as part of the study but were unaware of the specific oxygen regimen. They were aware that the patients referred to them had abnormal screening tests, persistent symptoms, or had undergone deterioration in their test scores, based on the study protocol. Clinical psychologists classified patients as normal, mildly abnormal, moderately abnormal, and severely abnormal.

Individuals who were initially normal after treatment, and then deteriorated in their cognitive function in two or more of the tests were classified as having DNS. Patients with DNS were referred for formal neuropsychiatric testing, followed by five additional HBO treatments, as outlined in figure 14.1.

14.2.2. Outcome analysis at 3 months - detailed neuropsychological testing

Follow-up occurred at three months post treatment. Neurological and cognitive outcomes at 3-month follow-up were recorded as good (normal), or poor (PNS, DNS or death). Those who had returned to their usual employment or activities, had no ongoing symptoms and normal screening tests were classified as “good” outcomes. These patients were discharged and received no further follow-up.

Allocation to “poor” outcome groups (PNS or DNS) was based on the detailed assessments made by the clinical psychologists. They were classified as mild PNS (one test abnormal), moderate PNS (two

or three tests abnormal), severe PNS (more than three tests abnormal, or significant neurological abnormality). Delayed neurological sequelae required deterioration in one or more test scores for its identification. Any patients who died within 3 months of treatment were also classified as poor outcomes. The three-month test scores were recorded as the official study outcomes for the patients. The three-month outcome was then compared to the neurological status of the patient at the point when ECO became unrecordable, to assess if this was a reliable marker of treatment endpoint.

14.3. Results

Study Population

A total of 66 patients were eligible for entry into the study. These consisted of 52 males and 14 females. The exposure to CO was as a result of deliberate self-harm (DSH) in 44 cases (40 males, 4 females), the domestic environment in 20 cases (10 males, 10 females), and 2 males were exposed in industrial environments. The study population was described in more detail in the summary table, appendix 18.1.

14.3.1. Neurological status at entry

Forty subjects experienced LOC, and six of these were still comatose upon arrival in the ED. One initially comatose patient was referred three weeks after the poisoning, because his acute CO poisoning was not recognised. This patient had developed DNS, having been discharged from hospital apparently normal, and was not treated acutely using our study protocol. He was therefore not included in data analysis. One patient with LOC refused to enter the study when he regained consciousness, and was not transferred to Fremantle Hospital. His status was unknown. Twenty-seven subjects with LOC had either impaired consciousness (11 patients), or impaired cognition (16 patients), when assessed in the ED. The remaining six with LOC had improved to have normal MMSE in the ED.

Of the 26 individuals who were stated not to lose consciousness (or there was doubt if LOC), three had impaired consciousness when assessed in the ED, and seven had impaired cognition. One of these patients refused to enter the study, when his mental state cleared after breathing NBO. Sixteen had normal MMSE scores. Of these, one refused to enter the study, and fifteen had no significant signs of cognitive dysfunction in the ED.

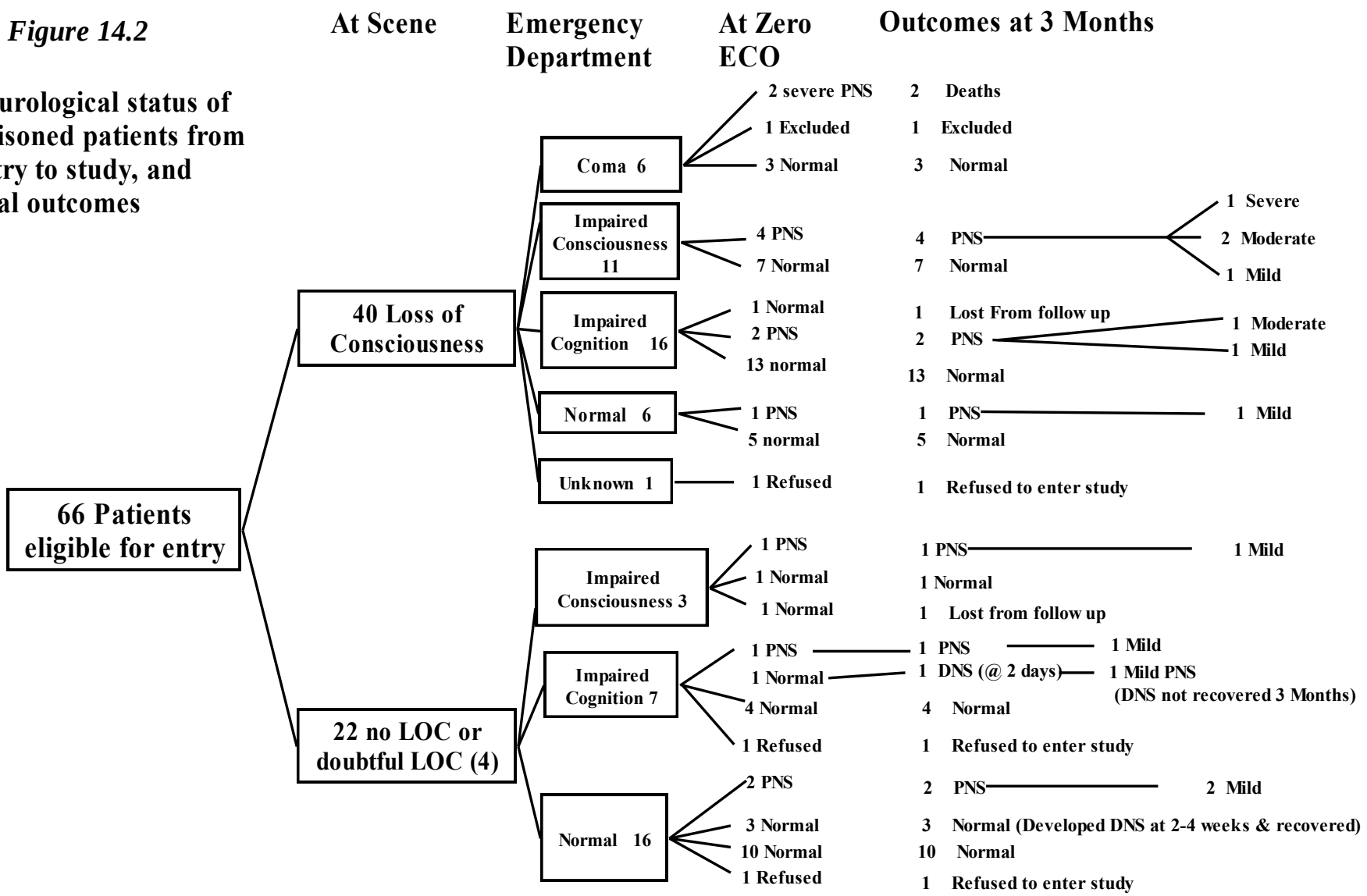
The individual excluded due to late referral, and three patients who refused to participate, were all treated with NBO. The known details of their clinical courses are described later in figure 14.2.

14.3.2. Outcomes across the study time line

Figure 14.2 shows the neurological status of the patient population from the point of rescue to the point of outcome assessment.

Figure 14.2

Neurological status of Poisoned patients from entry to study, and final outcomes



Neurological status on arrival in the ED

Of the sixty two patients entering the study, 44 were able to undertake a MMSE, and the mean score was 24.1/ 30, SD = 7.3 (95% CI 22.1 to 26.0). Twenty-three patients had abnormal MMSE scores ≤ 25 when tested in the ED, one of these refused to enter the study. Two out of the 62 patients were unable to receive follow-up. Patients reported the following symptoms on arrival in the ED; headache (32 patients), dizziness (17 patients), weakness (13 patients), nausea and/or vomiting (13 patients), and visual disturbances were noted in 3 patients.

14.3.3. Allocation to treatment group

Allocation in accordance with study protocol

Fifty-eight of the 62 patients (94%) were allocated to treatment in strict accordance with the study protocol. Three patients received treatment with HBO despite no LOC, and their neurological examination and cognitive function was apparently normal when assessed in the ED. There was some doubt over whether or not one of these patients had actually lost consciousness. The other two without LOC were adult family members exposed to CO in two separate incidents. Each underwent HBO treatment to accompany their more severely affected children.

One patient should have received HBO according to the study protocol, but could not tolerate pressurisation. This patient, an 8-year old child, was allocated HBO after appearing to have mild cognitive impairment. The child could not tolerate HBO due to ear pain, hence was treated with NBO.

ECO and allocated treatment

To determine if there were significant differences in ECO at study entry patients were split according to their allocated treatment group. The results are summarised in table 14.4. There were no significant differences in ECO between the two treatment groups, at the commencement of treatment, although there was a trend towards higher ECO values in the group allocated to HBO.

Table 14.4 Mean ECO (air and O_2) prior to study entry at Fremantle Hospital

Parameter	Treated with NBO	Treated with HBO	P value
Mean ECO air (ppm) (95% CI)	2.9 (0.9 to 4.9)	19.9 (7.3 to 32.5)	0.14
Mean ECO O_2 (ppm) (95% CI)	11.8 (4.9 to 18.6)	44.4 (22.9 to 66.0)	0.12

14.3.4. Delay to study entry and initial oxygen treatment

There was a mean delay of 12.0 hours (95% CI = 7.9 to 16.0) before study entry for patients treated with HBO, compared with 6.7 hours (95% CI = 1.1 to 12.5) for the group treated with NBO. This delay for HBO treated patients due to transfer from other hospitals was not statistically significant (p=0.23). There was no significant difference in delay to initial oxygen treatment for the NBO (5.8 ± 2.6 hours) and HBO (5.6 ± 1.5 hours), p = 0.94.

ED Neurological status and allocation to treatment

As a means of auditing whether or not patients were allocated in accordance with study protocols, the allocation to treatment groups was compared with neurological ranks in the ED. Figure 14.3 shows the allocation to treatment group according to neurological rank, at the time of arrival in the ED. This excludes one patient who refused to enter the study, whose ED neurological status was not known. The patient with a neurological rank 1, treated with NBO was excluded due to being referred non-acutely with DNS (see 14.3.6 and appendix 18.7).

The difference in ranks for the group allocated to NBO compared with HBO was highly significant: p < 0.0001 using two tailed Mann Whitney test, U= 76.0.

Figure 14.3 ED patient neurological ranks and treatment allocation for 65 patients

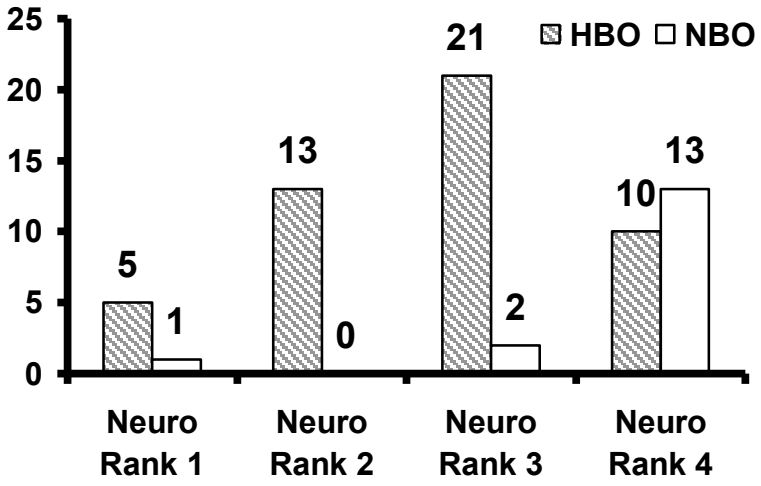


Table 14.2 shows the relative proportions of individuals who had LOC, classified by treatment allocation. There was a highly significant difference in the proportions of patients with LOC, when allocated to treatment groups, using Fisher's exact test, $p<0.0001$.

Table 14.2 - Loss of Consciousness and treatment allocation

	Treatment group (n = 62)	
Clinical Effect of CO	**NBO**	**HBO**
No loss of consciousness	13	10
Loss of consciousness	0	39

Deliberate versus accidental CO exposure and allocation to treatment group

Individuals with deliberate exposure to CO were more likely to be allocated to the Hyperbaric Oxygen treatment group, than those accidentally poisoned, $p = 0.0006$ by Fisher's exact test. This is summarised in table 14.3. The odds ratio for treatment with HBO (deliberate exposure versus accidental) was 9.4 (95% CI = 2.7 to 32.8).

Table 14.3 Deliberate versus accidental CO exposure and treatment allocation

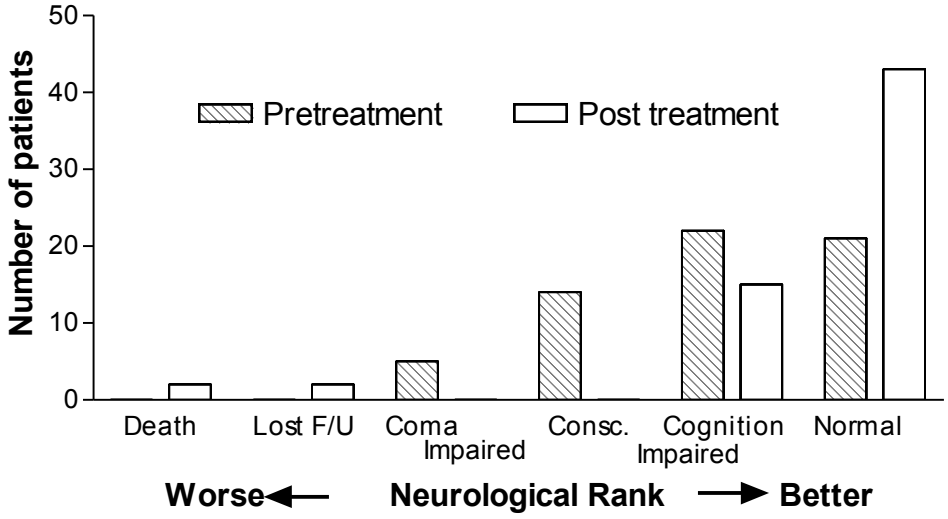
Intent of CO exposure	Allocated treatment group (n = 62)	
	NBO	HBO
Deliberate	2	39
Accidental	11	10

Tables 14.2 and 14.3 exclude three patients who refused to participate in the study (all deliberate self-harm), and one who presented three weeks after poisoning.

14.3.5. Effect of treatment on neurological rank

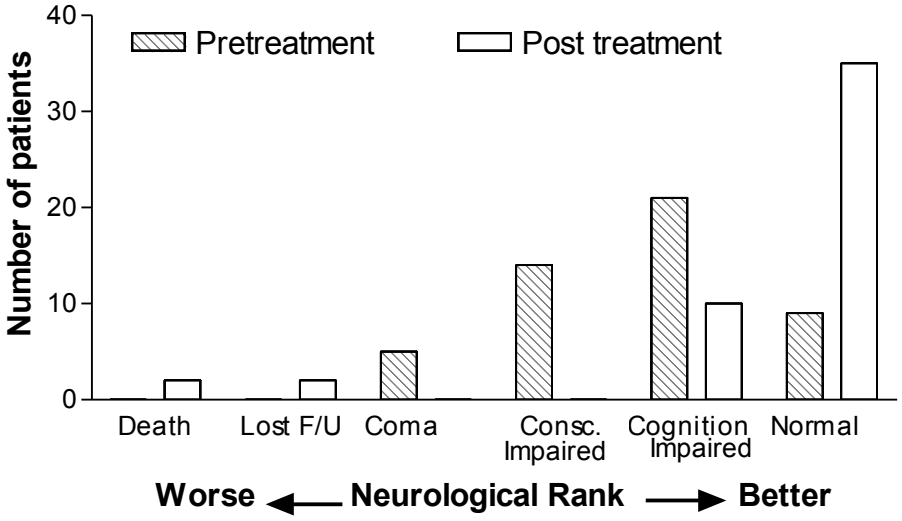
Patients lost to follow-up were classified as a neurological rank worse than coma, for the purposes of post treatment outcome analysis. For the study population, there was a statistically significant improvement in neurological ranking after treatment. Despite classifying patients lost to follow-up to a worse neurological rank, there was a statistically significant improvement in neurological rank using the Wilcoxon signed rank test, p=0.002. Sum of signed ranks W=463.0. These are summarised in figure 14.4.

Figure 14.4 Neurological rankings before and after treatment (n=62)



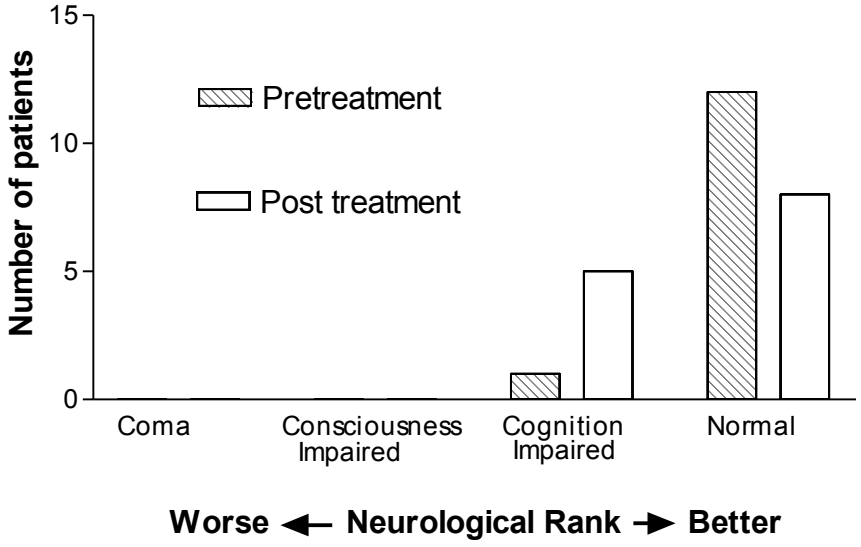
Figures 14.5 and 14.6 demonstrate the neurological rankings of patients before and after treatment, split by the treatment received.

Figure 14.5 Neurological ranks pre and post HBO treatment (n=49)



There was a significant improvement in neurological rank after treatment with HBO, $p = 0.01$, using the Wilcoxon signed rank test, sum of signed ranks W=393.0.

Figure 14.6 Neurological ranks before and after NBO treatment (n = 13)



For the group treated with NBO however, there was no significant change in neurological ranks detected using the Wilcoxon signed rank test, $p = 0.16$, sum of signed ranks = -14.0. After treatment, there was no significant difference between ranks between HBO and NBO treated groups ($p = 0.56$, Mann Whitney U test, U = 279.0).

14.3.6. Detailed description of refusals, lost to follow-up and deaths

Appendix 18.1 summarises selected features of the patients enrolled in this series.

Four of the patients were not formally enrolled in the study, and two were lost at follow-up. These are included in table so that their outcomes could be described with as great a detail as possible. There were two deaths, and both were included for outcome analysis. Late entry was defined as enrolling in the study greater than 12 hours after rescue from CO.

Patients refusing to enter study

Of the 66 patients, three refused to participate in the study. These were males (ages 23, 25 and 35), all had CO exposure as a result of deliberate self harm.

Excluded because significantly outside treatment protocol

One patient was referred three weeks after his CO poisoning. This case is described in more detail in appendix 18.7, as it demonstrates the clinical features of severe DNS, with recovery.

Patients lost to follow-up

Two patients did not receive face-to-face follow-up. They were included in the entry criteria analysis, but only included in the outcome analysis as a neurological rank worse than coma (assuming a worst possible outcome on an intention-to-treat basis.

1. A 30 year-old male who received exposure to CO as an act of deliberate self-harm. He lost consciousness during the exposure. He presented late for treatment, 26.5 hours after the exposure. At this time his COHb was 1.5%, and CK level was very high (43,575) consistent with rhabdomyolysis, and suggesting a long period of unconsciousness. His presenting MMSE was 30/30. He received two treatments with hyperbaric oxygen. Follow-up was only possible by telephone interview, as he had moved 4000 km away to Queensland (Australia) to get away from the domestic situation that precipitated his suicide attempt. He had no errors on telephone MMSE, and stated he had no ongoing symptoms or functional problems.

2. A 41 year-old male who received exposure to CO as an act of deliberate self harm. He did not lose consciousness during a 1 hour exposure to CO. His initial COHb was 17%, and MMSE 24/30. He

was treated with 100% oxygen 2.5 hours after his exposure, then Hyperbaric oxygen at 9 hours after exposure. The delay between initial NBO treatment and HBO was due to the patient absconding from hospital then being returned after two hours. He received two treatments with HBO, and had normal post treatment MMSE and screening tests. He attended follow-up at one month, and again his screening tests were normal. He was unable to be traced for three- month follow-up and hence a definite outcome was not known for the patient.

Deaths

There were two deaths in the series. These were included in the entry criteria analysis, because they were enrolled prospectively. These were included in the data for outcome analysis.

1. A five year-old girl who was the victim of deliberate exposure to CO with her father as part of the father's suicide attempt. When she failed to succumb to the CO exposure, the child was then seriously wounded with a stabbing to the chest and neck, which lacerated her right carotid artery. Her COHb was 6% in the ED, and she required emergency surgery for the stab wounds, followed by 24H of ventilation with 100% oxygen. She then received two treatments with HBO at 2.8 ATA (ventilated). She had zero CO in the breath. She died two days later of a massive right hemisphere brain infarct, due to the lacerated carotid artery. CO poisoning was not the primary cause of death.

2. A 30 year-old male who had a prolonged exposure to CO as an act of deliberate self-harm. He was intubated and ventilated with 100% oxygen and hour after rescue, and had a prolonged transport from a remote area of Western Australia to Fremantle Hospital. He received continuous 100% oxygen, until he was treated with HBO 12.25 hours after rescue. He showed no improvement after five hyperbaric oxygen treatments. He reached zero CO offgassing after the third HBO treatment. He continued to excrete CO at levels higher than controls, for the last two HBO treatments, despite remaining on 100% oxygen between treatments, and demonstrated unrecordable COHb levels. After completing 5 HBO treatments, he was quadriparetic, incontinent of urine and faeces, with a Glasgow Coma Score of 11. CT scan of the brain demonstrated widespread loss of grey/white matter differentiation consistent with hypoxic injury. It was not possible to test his cognitive function. He was admitted to a rehabilitation ward and subsequently died of pneumonia two months later. The cause of death was pneumonia secondary to loss of airway protective reflexes, secondary to hypoxic brain injury from CO poisoning.

Late referrals

Of the 60 patients with complete follow-up, sixteen were referred later than 12 hours after CO exposure. This included the two patients who died. They were also referred for entry into the study prospectively, and received the correct treatment according to the study protocol. This group was identified for outcome analysis, as previous studies have suggested that delays in receiving HBO may affect outcome.

14.3.7. Comparison of neurological status at zero ECO with outcome at 3 months

The neurological status of the patients when zero ECO was reached and their final outcomes are shown in figure 14.2 and table 14.5. Of the 60 patients with full follow-up data, 17 had poor outcomes (28.3%), despite all treatment provided. After treatment to an end-point of unrecordable ECO, 13 patients were initially assessed as having PNS. All received a prolonged course of HBO until their condition plateaued. Three of these patients had normal MMSE scores in the ED, however the more detailed screening post treatment revealed abnormalities in cognitive function. All 13 received an extra course of HBO until their condition plateaued. Of the 13 patients with PNS at the end of treatment, two died, and the remaining 11 had persistent cognitive abnormalities when tested at 3 months. Forty-nine patients had normal cognitive screening at the end of treatment, however, 4 of these developed DNS (see below). They were grouped with the cases of PNS, and deaths, as poor outcomes. In order to determine whether or not a "good" neurological status of the patient at the completion of treatment (zero ECO) was predictive of "good" final outcome, the data was arranged into a 2 x 2 contingency table as follows:

Table 14.5 Neurological Status after reaching zero ECO, compared with final outcome at three months

	Final Outcome at three months POOR	Final Outcome at three months GOOD	TOTAL

Neurological Status after reaching zero ECO = Abnormal (POOR)	True Positives 13	False Positive 0	13
Neurological Status after reaching zero ECO = Normal (GOOD)	False Negative 4	True Negatives 43	47
TOTAL	17	43	60

For the above table, the *sensitivity* of the neurological status at zero ECO = 0.82. The *specificity* for this assessment = 1.0. The *positive predictive value* = 1.0 and the *negative predictive value* = 0.94. If patients had abnormal cognitive function or neurological status when tested at the chosen study end-point of unrecordable ECO, then they continued to be abnormal at 3 months. The extra HBO treatments at the chosen dose did not appear to make a difference.

All cases of DNS were treated with a further five HBO treatments, and three out of four recovered. None of the group suffering DNS had lost consciousness, and three out of the four were initially treated with NBO. The time of onset of DNS is also shown in table 14.6. This time was only approximate because it was confirmed at follow-up. One patient was detected at two days post-HBO, and three other cases of DNS were detected at one month. The delay between CO poisoning and treatment is recorded in table 14.6.

All cases of DNS had received oxygen within six hours of poisoning, and only one patient initially satisfied criteria for HBO, which he received at 18 hours post poisoning. Three of these DNS cases were successfully retreated with HBO, and the psychometric deficit cleared. The remaining case of DNS evolved into PNS by 3 months, and was not predicted by his neurological status at the end of treatment when he reached unrecordable ECO. This individual was a 42 year old male who received late HBO treatment (>12 hours). He had normal screening tests at zero ECO. He then deteriorated within two days of treatment, was retreated with further HBO, and became normal but demonstrated mild PNS at three-month follow-up. He had actually returned to work at the time of his follow-up, but complained of not managing his routine tasks. He was the only case of DNS that did not recover fully at the study end-point.

Table 14.6 Delay to onset of cases of DNS compared with treatment delay

Case ID	Onset of DNS	Delay from CO Poisoning to treatment	Treatment
C4348566	1 month	3 hours	NBO
H0405258	1 month	5.5 hours	NBO
L2204465	1 month	1.5 hours	NBO
K0134407	2 weeks	3.0 hours 100% O2 HBO at 18 hours	HBO

14.4. Discussion

In this case series, it was possible to obtain accurate follow-up data for 91 percent of patients at three months. This compares favourably with other series of CO poisoned patients. The follow-up rates for other recent clinical series were as follows: Raphael et al (1989), 89% at one month, Gorman et al (1992) 76% at one month, Ducasse et al (1995), 69% at one month, Thom et al (1995), 100% at 3 months, Mathieu et al (1998), 100% at 12 months, Scheinkestel et al (1999), 46% at one month and Weaver et al (2000) 95% at 6 weeks. My study entry protocol included all patients with CO poisoning, referred for assessment at Fremantle Hospital.

Patients treated with HBO were received from the whole of Perth metropolitan area (population 1.2 million). There were specific criteria for referral for HBO, so this created a bias between the number of patients who received HBO versus the number treated with NBO at Fremantle Hospital. More severely poisoned patients were referred from other hospitals to Fremantle Hospital for hyperbaric oxygen treatment. Less severely poisoned patients were treated at their own facilities with NBO, and this group was not entered into the study. Patients arriving at Fremantle hospital were not randomized. As a result, the number of HBO treated patients (n=49) in this series, was greater than the number of NBO treated patients (n=17). The latter group derived solely from CO poisoned patients presenting to Fremantle Hospital (referral base approximately 200,000 population).

Based on this, it is estimated that there may have been an additional 85 treated with NBO at other centres, patients, ie 17 x (1.2 million – 200,000)/200,000 during the study period. I did not seek to identify those patients.

When initially assessed in the referring ED, the group referred for HBO treatment had clinically more severe poisoning, and most likely, higher initial body stores of CO. Higher initial COHb levels measured in the referring ED supported this. It was not possible to obtain ECO measurements for all cases at their initial Emergency presentation because of the widespread geographic locations of the Perth Metropolitan Hospitals. The delays in entry to the study for the group allocated HBO treatment were due to inter-hospital transfers - on some occasions via two hospitals. During transfers individuals received 100% oxygen (they had been identified as needing referral to Fremantle Hospital), and hence were reducing their body stores of CO. Although not statistically significant, these delays were clinically important.

At study entry, there was no significant difference between ECO values in the two treatment arms, although there was a trend for higher ECO in the patients allocated to HBO treatment. Despite the lack of significant difference in ECO levels between the two groups, the HBO treated group remained neurologically more impaired than the NBO group at study entry, suggesting a "lead time" between initiation of treatment, and recovery.

The potential implications for patient outcomes with treatment delays are quite significant, and are discussed further in the chapter 15. The delays placed most patients outside the "ideal" 6 hours to HBO treatment suggested by Goulon et al (1986). Other authors have used 12 hours as their study entry criteria to receive HBO, without apparent ill effect (Raphael 1989, Mathieu et al 1998). More recently, Weaver used 24 hours as entry criteria, and still demonstrated benefit from HBO, however over two thirds of the patients were treated in less than 6 hours. Even those treated greater than 6 hours had mean times to treatment of 8.6 ± 3.4 hours (HBO) and 9.0 ± 3.8 hours (NBO) (Weaver et al 2002).

Ninety four percent of patients were allocated to their treatment group in accordance with the study protocol. The four protocol violations were described in the results, and all had good outcomes with no sequelae. Individuals allocated to receive HBO treatment had significantly neurological ranks at presentation compared with those allocated to HBO. This difference provided support that the prospective treatment allocation was mostly in accordance with protocol. In keeping with this apparent greater degree of poisoning, suicidal patients were more likely to be allocated to HBO treatment. More severely poisoned patients were allocated to receive HBO. It is not surprising therefore that an improvement in neurological rank was noticeable for the HBO treated population.

The patients treated with NBO did not have a significant change in their neurological rank. This was also likely to be an effect of the selection process, because the group were initially assigned to NBO because they did not have significant neurological or cognitive deficits. Twelve of the thirteen patients treated with 100% oxygen had normal cognitive function when assessed in the ED, and their rank did not alter after treatment. After treatment, there was no significant difference between neurological ranks of patients treated with NBO and HBO, suggesting the HBO treated population had improved enough to become indistinguishable from the NBO treated population.

Despite the assumption by other authors that oxygen treatment is beneficial, this acute treatment benefit has not been documented previously. It cannot be said however, that the improvement was specifically due to HBO treatment, as we did not have a control arm receiving no treatment. From available literature, Smith and Brandon (1973) determined that with no oxygen treatment, some 36 percent of CO poisoned individuals have severe sequelae when followed up to three years. I have been unable to identify any comparative or randomized studies of CO poisoning that have had an air treatment group.

The MMSE had limitations, and could only be applied to patients who were conscious and talking. The MMSE test is also non-specific, detecting impairment due to other causes, for example co-ingestions. For the purposes of the study, it was considered better to assume that the abnormality of cognition was due to CO, for the purposes of the study. The limitations of the MMSE created the need for the neurological ranking system to track individuals who could not cooperate for testing. Due to its design, the MMSE also could not be used in children who were under the age of 10 years. We relied on parents' and school reports for assessing outcomes in the children in the series, particularly at the three-month follow-up.

The severity of poisoning in this case series is comparable with other studies. Thirty percent of our patients presented to Fremantle ED in coma, or with impaired consciousness, compared with 10 percent in Raphael et al's 1989 series, and 59 percent in Scheinkestel's 1999 series). Sixty-one percent of individuals in my study lost consciousness at some stage, and there was a 3% mortality rate. Deaths were reported in only four of eight major comparative trials in the last 17 years: Mathieu's 1985 study reported a death rate of 1.7%, Scheinkestel et al (6/191 =3.1%), Raphael et al (4/629 = 0.7%) and Weaver reported no deaths in the clinical trial, however there were four deaths in individuals not enrolled out of a possible 322 eligible patients (1.2%) (Mathieu et al 1985, Raphael et al 1989, Scheinkestel et al 1999, Weaver et al 2002).

Scheinkestel et al defined severe poisoning as any of MMSE score ≤ 24, confusion, focal neurological deficits, loss of consciousness, ECG abnormalities, arrhythmias, COHb > 30%, metabolic acidosis, hypotension, convulsions, or cardiac arrest. Seventy three percent of patients in Scheinkestel's series had severe poisoning (Scheinkestel et al 1999). The cases in my series are comparable in severity, with (50/66 = 75.7%) of patients severely poisoned. When patients in my series able to undertake a mini-mental state examination in the ED, the mean scores (24.1/30, 95% CI = 22.1 to 26.0) were lower than

those observed by Scheinkestel et al (27.0/30, 95% CI = 26.1 to 27.9). In my series, 66.7% of poisonings were due to deliberate self-harm, compared with 68.5% in Scheinkestel's series. Hence there are similarities between my series, and Scheinkestel's, as each is derived from an Australian State Capital City referral centre, during the 1990's.

My study data demonstrates that reaching zero ECO did not represent a cure for all CO poisoned patients, because 17 out of 60 (28.3%) had poor outcomes (2 deaths, 11 PNS and 4 DNS). Patients with PNS are likely to have sustained irreversible (at least in part, hypoxic) injury at the time of their poisoning. Given the severity of CO poisoned patients in my series, patient outcomes are consistent with, or better than those found by other authors. Raphael's group showed that between 34 and 48% of patients had not fully recovered from CO poisoning at one-month follow-up (Raphael et al 1989). Gorman and colleagues demonstrated an overall abnormality rate of 31.6% at one-month follow-up (Gorman et al 1992).

Thom et al (1995) determined that 22% of patients treated with 100% oxygen for acute non-coma producing CO poisoning developed delayed abnormalities of psychometric function at one month. Scheinkestel et al (1999) showed very high rates of abnormalities in cognitive function, 75.5% overall. Our overall outcome of 28.3% abnormalities at 3-month follow-up is reasonable, given the similarities in case mix and severity of CO poisoning compared to the Scheinkestel et al series. This provides supportive evidence that zero ECO may compliment other methods of determining end-point for treatment of CO poisoning.

Another important finding of our study is that the neurological and cognitive status of the patient assessed when they reach zero ECO, appears to be predictive of outcome. The patients' neurological and cognitive status at the time of completion of treatment had high specificity, positive and negative predictive value of final outcome. However it had moderate sensitivity, indicating that the status at zero ECO is not as effective at ruling out a poor outcome, as it is at identifying poor outcomes. In my study, poisoned patients who had abnormal status at completion of treatment using unrecordable ECO as a treatment end-point, were also likely to have abnormal status at 3 months. This did not appear to be altered by additional HBO treatments provided in the study protocol. Patients with normal psychometric status after treatment to zero ECO end-point, had a 43/47 (=91%) chance of being normal at 3 months follow-up.

My data indicate that it is important to provide follow-up of apparently normal CO poisoned patients, to detect cases of DNS. The four patients who developed DNS were in essence, false negative results for using ECO as a treatment endpoint. They would have been missed if follow-up had not been provided. They provide evidence that treatment to an end-point of unrecordable ECO, does not prevent DNS. It also suggests that DNS may result from factors other than just CO toxicity. A test that identifies patients who will develop DNS has not yet been identified.

The data in this chapter suggest that treating acutely poisoned patients until they have unrecordable ECO may compliment other methods of determining end-point for treatment of CO poisoning. Patients who are abnormal at this point may be referred for rehabilitation, as they are unlikely to be restored to normal cognitive function by further oxygen treatment. Patients who are normal at the treatment end-point still require follow-up and cognitive testing.

14.5. Conclusions

The results of this clinical series demonstrate that treatment of acute CO poisoning using unrecordable ECO as an end-point, correlated well with acute clinical improvement of the patient, when measured by improvement in neurological rank. The case series provides evidence that unrecordable ECO may compliment existing methods to guide treatment end-point. The case series was of equivalent or worse clinical severity than recent published series, however outcomes measure with psychometric testing were as good or better than those series. Adverse neurological outcomes at 3 months were predicted by the neurological status of the patient at the specified treatment end-point when ECO was unrecordable. This was an important finding, as it provided support for the use of zero ECO as a marker of treatment end-point, however to fully test this hypothesis, would require a larger prospective randomized controlled trial.

Normal neuropsychological status at zero ECO did not however predict patients who developed DNS. This indicates that close follow-up of normal patients; using cognitive function screening is still required in the first 4 – 6 weeks after treatment.

It appears that there will always be a percentage of CO poisoned individuals who will have poor outcomes, due to permanent (probably hypoxic) damage occurring at the time of the poisoning. To prevent these poor outcomes requires primary prevention of exposure to CO, more rapid detection, and the earliest possible treatment oxygen. A follow-up randomized controlled study trialing different oxygen doses for patients after acute CO poisoning, comparing unrecordable ECO with other treatment end-points may provide a definitive answer to the question, "*Is unrecordable ECO a useful treatment end-point in acute carbon monoxide poisoning*?"

15. EVALUATION OF FACTORS INFLUENCING OUTCOME IN THE CASE SERIES OF CO POISONED PATIENTS

Introduction

Apart from ECO, there were many factors identified at entry to the study that may have also influenced final outcome for the case series of patients studied as part of this research. These factors were investigated in this chapter to see if they affected outcome for the poisoned individuals.

15.1. Aims

The aims of this chapter were:

(1) To determine whether demographic factors, aetiology and severity of poisoning, ECO, delays to treatment and method of treatment had any relationship to outcomes at 3 months.

(2) To determine if patients' own reporting of symptoms and health status had any relationship with outcomes

15.2. Methods

The variables collected at the entry to the study that related to the patient were compared with the outcomes in this chapter of the study. The entry variables included: demographics (age, sex, deliberate or accidental, smoking status, concomitant use of alcohol/drugs), severity of poisoning (neurological rank, initial COHb, acidosis and ECO measurements), delays to treatment and study entry, and the treatment administered. In addition, two questionnaires assessing patients' functional status and their general health were administered at the time of outcome assessment, to control for psychological distress which may have been associated with attempting suicide. Outcomes were assessed at three months after poisoning, by neuropsychologists as defined in chapter 14. These were classified as good (normal neuropsychological screening and normal functioning, or normal neuropsychological testing), and poor (any of PNS, DNS, or death). Delayed neurological sequelae

and PNS were also assessed individually, to determine if there were specific entry factors that may have affected the outcome. The entry features, questionnaires and outcomes are summarized in table 15.1.

Table 15.1
Entry and outcome variables for the case series of CO poisoned patients

Entry Variable
Age
Sex (Male or Female)
Aetiology of CO Exposure (Deliberate or Accidental)
DRUGS / ALCOHOL USE AT TIME OF EXPOSURE (YES OR NO)
Smoking status (Yes or No)
Neurological rank at entry (1 to 4)
Initial COHb
Acidosis (pH < 7.32)
Entry ECO measurement breathing air
Entry ECO measurement breathing O2
Delay to oxygen treatment (hours)
Delay to study entry (hours)
Treatment method (NBO or HBO)

Outcome Status	
GOOD	Normal
POOR	Death
	PNS
	DNS

The above entry variables were assessed individually to determine if there was any association with outcomes. Two additional assessments were made at the time of three-month follow-up to determine if patient self-reporting of adverse symptoms correlated with outcome. The functional status questionnaire (FSQ, appendix 18.3) covered symptoms that could be indicative of CO-related neuropsychological dysfunction. The reason for administering the questionnaires was to see if patients' self-reporting correlated of symptoms correlated with the results of the detailed cognitive function assessment. The general health questionnaire (GHQ -12, appendix 18.4) covered symptoms that could be due to psychological distress. The numbers of abnormal responses in the FSQ, and negative symptoms in the GHQ were recorded in the study database. Scores for the FSQ and the GHQ-12 were then compared for patients who had poor outcomes (excluding deaths and those unable to cooperate) and those with good outcomes, to determine if there was any association.

15.3. Results

15.3.1. Entry variables and association with good and poor outcomes

Sixty patients had full follow-up for outcome analysis (91%). These consisted of 46 males and 14 females. Of the 60 patients, 13 received NBO, and 47 received HBO treatment. By three months, two patients had died (3.3%), and 58 were able to receive face-to-face follow-up assessment. The two deaths were classified as poor outcomes for the HBO group. Both the deceased patients had received prolonged treatment with NBO, and also HBO. The entry features were tabulated and compared to two specific outcomes; good and poor in tables 15.2 and 15.3. In some cases, complete data was not available, and analyses were conducted using available data. The numbers in each group are shown in brackets in the table.

Table 15.2 Entry criteria related to good and poor outcomes for 60 patients able to receive follow-up

Criterion at study entry	Good Outcome (n=43)	Poor Outcome (n=17) Death, PNS, or DNS	Statistical Test	P Value	Comment
Age	25.6 ± 1.9 (n=43)	28.6 ± 3.1 (n=17)	two tailed t test t=0.85, df = 58	0.40	Not significant
Sex	Female = 11 Male = 32	Female = 4 Male = 13	Fisher's Exact Test	1.00	Not significant
Exposure duration where known or estimated (Hours)	3.4 ± 0.4 hrs (n = 43)	2.3 ± 0.8 hrs (n = 14)	two tailed t test t=1.36, df = 55	0.18	Not significant
Duration of Loss of Consciousness where known	56.5 ± 15.1 minutes (n=43)	58.5 ± 26.7 minutes (n=14)	two tailed t test t=0.07, df = 55	0.95	Not significant
Neurological Rank when arriving in the ED	3.1 ± 0.9 (n = 43)	2.9 ±1.1 (n = 17)	Mann-Whitney Test	0.54	Not significant
Use Drugs/alcohol with exposure YES NO	14 29	8 9	Fisher's Exact Test	0.38 OR = 0.54 95% CI= 0.17 to 1.71	Not significant
Smokers YES NO	17 26	8 9	Fisher's Exact Test	0.77 OR = 0.74 95% CI = 0.24 to 2.28	Not significant
Aetiology = Deliberate self harm YES NO	26 17	13 4	Fisher's Exact Test	0.37 OR = 0.82 95% CI= 0.61 to 1.12	Not significant
COHb at study entry	10.3 ±1.7 (n=42)	12.8 ± 3.8 (n=17)	two tailed t test t=0.71, df = 57	0.48	Not significant
CO Measured in breath, breathing air	16.9 ± 5.7 (n = 38)	12.8 ± 10.5 (n = 16)	two tailed t test, t=0.37, df = 51	0.71	Not significant
CO measured in breath breathing O_2	40.9 ± 10.8 (N = 42)	21.5 ± 17.7 (N=17)	two tailed t test, t = 1.04, df = 57	0.30	Not significant
Acidosis (pH<7.32) YES NO	5 38	9 8	Fishers exact test	0.002 OR = 0.12 (95%CI= 0.03 – 0.44)	SIGNIFICANT

Table 15.3 Entry criteria related to good and poor outcomes for 60 patients able to receive follow-up

Criterion at study entry	Good Outcomes n=43	Poor Outcomes n=17 Death, PNS, or DNS	Statistical Test	p value	Comment
Loss of Consciousness at any time YES	28	9	Fisher's Exact Test	0.40 OR = 1.66 95% CI= 0.53 to 5.19	Not significant
NO	15	8			
Unconscious in Emergency Dept YES	3	2	Fisher's Exact Test	0.62 OR = 0.56 95% CI= 0.09 to 3.71	Not significant
NO	40	15			
Previous Psychiatric History YES	24	9	Fisher's Exact Test	1.00 OR = 1.12 95% CI = 0.36 to 3.47	Not significant
NO	19	8			
Motor Vehicle Source YES	25	13	Fisher's Exact Test	0.24 OR = 0.43 95% CI= 0.12 to 1.53	Not significant
NO	18	4			
Leaded Petrol YES	16	9	Fisher's Exact Test	0.38 OR = 0.53 95% CI= 0.17 to 1.64	Not significant
NO	27	8			
Time to zero CO (minutes)	208.2 ± 20.3 (n=41)	262.8 ± 71.2 (n=16)	two tailed t test, t= 1.00, df = 55	0.32	Not significant
Entry to study ≤ 12 Hours ≤ 12H	35	8	Fisher's Exact Test	0.01 OR = 4.92 95% CI= 1.45 to 16.7	SIGNIFICANT
> 12 H	8	9			
HBO SUBSET (n=47) entry ≤ 12 H	27	4	Fisher's Exact Test	0.01 OR = 6.75 95% CI= 1.60 to 28.40	SIGNIFICANT
entry > 12 H	8	8			
Time to oxygen treatment	2.6 ± 0.4 (n=43)	11.7 ± 4.0 (n = 17)	two tailed t test, t=3.52, df = 58	0.0008	SIGNIFICANT
HBO SUBGROUP - time to HBO treatment (hours)	9.8 ± 1.3 (n=35)	25.4 ± 5.7 (n=12)	two tailed t test, t=3.89, df = 45	0.0003	SIGNIFICANT
HBO SUBGROUP Time to zero ECO (minutes)	178.4 ± 21.6 (n=33)	106.8 ± 20.5 (n=11)	two tailed t test, t=1.81, df = 42	0.07	Not significant

15.3.2. Study entry factors that did not significantly correlate with outcome

The following factors at study entry did not demonstrate a statistically significant correlation with final outcomes: individuals' age or sex, duration of exposure to CO, loss of consciousness, neurological rank in the ED, concomitant use of drugs or alcohol, smoking status, previous psychiatric history, motor vehicle source of CO, or the use of leaded petrol, initial COHb and ECO breathing air or oxygen. Whether or not patients were exposed to CO as a result of deliberate self-harm had no statistical relationship with outcome, despite the observation in chapter 14 that they had more severe poisonings.

15.3.3. Study entry factors that significantly correlated with outcome

Acidosis

Patients who demonstrated acidosis pH < 7.32, were more likely to have poor outcomes than those without acidosis. It was intended to also assess lactate levels as part of the study protocol, however the test was not generally available at Perth's peripheral hospitals. As a result of low compliance with ordering the test, the relationship between lactate and outcome was not investigated.

Entry to study greater than 12 hours

Nine out of seventeen individuals who entered the study later than 12 hours after poisoning had poor outcomes, compared with only 8 out of 43 patients enrolled within 12 hours of their poisoning. This difference was statistically significant, p=0.01 using Fisher's Exact Test. The relative risk of poor outcome if entry to study ≤ 12 H = 0.35 (95% C I = 0.16 to 0.75).

Time to oxygen or HBO treatment

The group with poor outcomes had significantly longer times before oxygen was administered in any form; 11.7 hours ± 4.0 compared with 2.6 hours ± 0.4 for the group with good outcomes. This was highly significant using a two tailed t test, p = 0.0008. For the HBO treated group who had poor outcomes, there was a significantly increased delay before receiving HBO. Mean delay for poor outcomes = 25.4 ± 5.7 hours, versus 9.8 ± 1.3 hours for good outcomes, p = 0.0003.

HBO Group - Treatment delay to HBO greater than 12 hours

A cut-off period of 12 hours was selected because it reflected findings of previous literature. A significantly worse outcome occurred when patients allocated to HBO had a treatment delay of greater than 12 hours. Eight out of 12 patients with poor outcomes had treatment delays > 12H, compared with eight out of 35 with good outcomes, p= 0.01, Fisher's Exact Test. Odds ratio for poor outcome if HBO received > 12 Hours = 6.95 (95% CI= 1.6 to 28.4).

15.3.4. Patient self reporting of symptoms correlated with outcomes

At three-month follow-up interview, patients completed the FSQ and GHQ-12 prior to undertaking any cognitive function screening. The results of the FSQ and GHQ-12 results are summarized in table 15.4 below. Individuals with poor outcomes had significantly more abnormal responses in the FSQ at follow-up, compared to the group with good outcomes. The group with poor outcomes also reported a greater number of negative symptoms in the GHQ-12 at follow-up.

Table 15.4 Correlation of questionnaire results administered at follow-up with outcomes

Criterion	Poor Outcomes n=17 Death, PNS, or DNS	Good Outcomes n=43	Statistical Test	P Value	Comment
FSQ: Functional Status Questionnaire score – abnormal responses	3.6 ± 0.9 (n=13)	0.4 ± 0.1 (n=43)	two tailed t test, t=6.1, df = 54	< 0.0001	SIGNIFICANT
GHQ-12: General Health Questionnaire Score - negative symptoms	5.8 ± 1.0 (n=13)	2.2 ± 0.4 (n=41)	two tailed t test, t=4.07, df = 52	0.0002	SIGNIFICANT

15.3.5. Analysis of specific outcomes; DNS, and PNS and Deaths

In an effort to identify factors correlating with specific poor outcomes, patients with DNS were analysed as a separate group from those with PNS/death. The reason for the separation was that the PNS/death group represented patients with permanent neurological injury, whereas the majority (three out of four cases) of DNS recovered after receiving further HBO treatment. The fourth patient who did not recover from DNS was grouped with the PNS patients for final outcome analysis.

DNS Outcome Group

Table 15.5 examines variables at study entry for the subset of patients who developed DNS. Deaths were excluded from this analysis, because the patients who died were unable to be assessed as to whether they developed DNS - they were so severely affected by the CO. There were no entry factors that were significantly associated with risk of developing DNS, apart from a trend towards greater age in individuals with DNS.

Table 15.5 Risk of DNS related to study entry variables (Deaths Excluded)

Criterion	Delayed Neurological Sequelae = Yes (n=4)	Delayed Neurological Sequelae = NO (n=54)	p Value
Age of Patient	35.0 ± 7.0 (95% CI = 23.8 to 46.2)	26.3 ± 12.3 (95%CI = 23.0 to 29.7)	p = 0.09 * Trend but NS t=2.23, df = 4
ED Neurological Rank	3.8 (95% CI = 3.0 to 4.0)	3.1 (95% CI = 2.8 to 3.3)	p = 0.12 ‡ Mann Whitney U = 57
LOC Yes LOC No	1 3	34 20	p = 0.29 † OR = 0.2 (0.02 to 2.02)
Previous Psych History Yes No	1 3	32 24	p = 1.00 † OR = 0.25 (0.02 to 2.56)
Suicide Attempt Yes No	1 3	35 19	p = 0.15 † OR = 0.18 (0.02 to 1.86)
Smoker Yes No	2 2	22 32	p = 1.00 † OR = 1.46 (0.19 to 11.12)
Drugs/Alcohol Yes No	1 3	21 33	p = 1.00 † OR = 0.52 (0.05 to 5.38)
Time to 100%O2 ≤ 12 H > 12 H	3 1	40 14	p = 1.00 † OR = 1.05 (1.01 to 10.95)
ECO Air	3.7 ± 2.3 (95%CI = 0.0 to 13.7)	16.4 ± 5.3 (95% CI = 25.7 to 27.1)	p= 0.57 * t = 0.57, df = 52
ECO Oxygen	18.3 ± 10.3 (95% CI = 0.0 to 62.8)	36.3 ± 8.9 (95% CI = 18.3 to 54.1)	p = 0.65, * t = 0.46, df = 57
Acidosis pH<7.32 Yes No	0 4	12 42	p = 0.57 OR = 0.38 (0.02 to 7.51)
Motor Vehicle Source Yes No	1 3	35 19	p = 0.15 † OR = 0.18 (0.018 to 1.86)

* Two tailed t test, † Fisher's exact test, ‡ Mann Whitney U test

Table 15.6 correlates entry criteria for the patients who had the worst outcomes, death or PNS. There was no significant association between these outcomes and patients age, smoking status, previous psychiatric history, loss of consciousness, or ECO breathing air or oxygen. Death or PNS were significantly associated with; acidosis, CO exposure due to suicide attempt, and CO from a motor vehicle source. Trends were noted for association of death or PNS with lower ED neurological rank and delayed time to study entry, but these were not quite significant.

Table 15.6 Entry criteria versus risk of Death or PNS

Criterion	Persistent Neurological Sequelae or death YES (n=14)	Persistent Neurological Sequelae or death NO (n=46)	P Value
Age of Patient	27.7 ± 3.7 (95% CI = 20.5 to 34.9)	26.1 ± 1.8 (95%CI = 22.6 to 29.5)	P= 0.69 * t = 0.40, df = 19
ED Neurological Rank	2.6 (95% CI = 2.1 to 3.2)	3.2 (95% CI = 2.9 to 3.4)	P = 0.09 ǂ Trend but NS Mann Whitney U = 226
ECO Air (ppm)	14.8 ± 12.9 (95% CI = 0.0 to 43.0)	15.9 ± 5.3 (95% CI = 5.2 to 26.7)	P = 0.62 * t = 0.49, df = 17
ECO Oxygen (ppm)	22.1 ± 15.4 (95% CI = 0.0 to 55.3)	39.4 ± 10.1 (95% CI = 19.1 to 59.8)	P= 0.18 * t = 1.34, df = 38
Acidosis pH < 7.32 Yes No	9 5	5 41	P = 0.0002 ǂ SIGNIFICANT OR = 14.76, (3.52 to 61.96)
LOC Yes No	9 5	28 18	P = 1.00 ǂ OR = 1.15, (0.33 to 4.01)
Time to Study ≤ 12 H Entry > 12 H	7 7	36 10	P = 0.087 ǂ Trend but NS OR = 0.28 (0.08 to 0.98)
Smoker Yes No	7 7	18 28	P = 0.54 ǂ OR = 1.55, (0.47 to 5.18)
Previous Psych History Yes No	8 6	25 21	P = 1.00 OR = 1.12 (0.33 – 3.74)
Suicide Attempt Yes No	13 1	26 20	P = 0.02 ǂ SIGNIFICANT OR= 10.0 (1.20 to 83.0)
Drugs/Alcohol Yes No	8 6	14 32	P = 0.11 ǂ OR = 3.04 (0.89 to 10.44)
Motor Yes Vehicle Source No	13 1	25 21	P = 0.01 ǂ SIGNIFICANT OR= 10.92 (1.32 to 90.58)

15.3.6. Entry variables and outcomes compared with treatment

Entry variables split by treatment are summarised in table 15.7. Because the study was not randomized, direct comparison between the groups is not strictly valid. These tables were included to examine if there were any unusual outcomes that required explanation. The HBO treated patients were more likely than those treated with NBO to: have a previous psychiatric history, be suicidal, have lost consciousness have taken alcohol and drugs, be acidotic, have higher COHb levels, lower neurological rankings in the ED and lower MMSE scores. There was a statistically insignificant trend towards higher ECO levels in the hyperbaric treated group. All findings were consistent with the study protocol for allocating more seriously poisoned patients into the HBO treatment group.

No significant association was noted between patients' age or sex and allocation to treatment. Despite having more severe poisoning, patients allocated to receive HBO had no difference in the stated exposure duration to the CO compared with those allocated to NBO. No other factors in table 15.7 were significantly different when comparing treatment groups.

The mean delay from rescue to confirmed NBO treatment for all 66 patients was 5.6 hours (SD 10.2, 95% CI = 3.0 to 8.3 hours). These delays included prehospital times, during which high-flow oxygen (but not 100%) was being delivered. There was no significant difference in the mean time to initially receiving NBO treatment, for the groups that were subsequently allocated to receive HBO or NBO in the prospective case series. Delays to study entry for HBO treated patients were not significantly longer than for NBO treatment.

Table 15.7 Entry features of poisoned patients, split by treatment groups (n=60 receiving follow-up)

Entry Features	HBO Treated (n=47)	NBO treated (n=13)	P Value	
Demographic				
Age	27.3 (24.0 - 30.7)	23.23 (14.1 - 32.4)	0.29	*
Sex	Male = 38 (80.8%)	Male = 8 (61.5%)	0.16	†
Suicide attempt	36 (76.6%)	2 (15.4%)	0.0001	†
Alcohol/drugs taken	25 (53.2%)	1 (7.7%)	0.05	†
Previous Psychiatric history	31 (66.0%)	2 (15.4%)	0.0016	†
Clinical severity criteria				
Exposure duration (h)	3.6 (2.4 - 4.8)	2.4 (0.7 - 4.1)	0.52	*
Number with LOC	37 (78.7%)	0	< 0.0001	†
Ventilated	5 (10.6%)	0	0.58	†
Acidosis (pH<7.32)	14 (29.8%)	0	0.029	†
COHb Level (%)	13.2 (9.34 – 17.08))	5.0 (1.6 - 8.4)	0.03	*
Delay to 100% O2 (hours)	5.6 (2.5 – 8.7)	5.8 (0.13 – 11.5)	0.94	*
Delay to study entry (hours)	12.0 (7.9 – 16.0)	6.7 (1.1 – 12.5)	0.23	*
Time to HBO (hours)	14.6 (10.6 – 18.5)	N/A		
Air ECO level (ppm)	19.9 (7.3 to 32.5)	2.9 (0.9 - 4.9)	0.14	*
100% O2 ECO level (ppm)	44.4 (22.9 to 66.0)	11.8 (4.9 - 18.6)	0.12	*
ED Neurological Ranking	2.8 (2.5 - 3.1)	3.9 (3.8 - 4.0)	< 0.0001	‡
Coma	5	0		
Impaired consciousness	8	0		
Impaired cognition	26	1		
Normal	10	12		
Mini-Mental State Score	19.7 (16.5 – 22.9)	29.6 (29.2 – 30.0)	0.008	*
Signs and Symptoms				
Coma	5 (10.6%)	0	0.58	†
Cardiac arrest	2 (4.3%)	0	1.00	†
Convulsions	2 (4.3%)	0	1.00	†
Headache	24 (51.1%)	8 (61.54%)	0.55	†
Visual impairment	3 (6.12%)	0	NS	†
Weakness	11 (23.4%)	2 (15.4%)	0.72	†
Nausea, vomiting	12 (25.5%)	1 (7.7%)	0.26	†
Confusion	22 (42.5%)	3 (23.1%)	0.33	†

* Two tailed t test, † Fisher's exact test, ‡ Mann Whitney U test

15.3.7. Outcome variables split by treatment

Table 15.8 shows the outcomes for poisoned individuals in the case series split by treatment. Because the study was not randomized, direct comparison between the groups is not strictly valid. Table 15.9 compares the outcomes (split by treatment) for patients treated less than 12 hours after poisoning

Table 15.8 Outcome criteria, comparing treatment groups

Criterion	HBO Treatment (n=47)	NBO Treatment (n=13)	Odds Ratio (95% CI)	p value
Time to unrecordable ECO	164.0 (144.8 - 183.2)	436.9 (376.0 - 497.8)		<0.0001 *
Deaths	2	0	OR = 1.48, (95% CI = 0.07 to 32.84)	1.0 †
Normal outcome	35/47	11/13	OR = 0.53 (95% CI = 0.10 to 2.74)	0.71 †
Persistent Neurological Sequelae	10/45	2/13	OR = 1.57 (95% CI = 0.30 - 8.29)	0.72 †
Mild	6	2		
Moderate	3			
Severe	1			
Delayed Neurological Sequelae	1/45	3/13	OR = 0.08 (95% CI = 0.007 - 0.81) Favours HBO	0.03 †
Return to previous occupation	36/45	10/13	OR = 1.2 (95% CI = 0.27 - 5.29)	1.00 †
Ongoing Psychiatric Morbidity	21/45 All suicidal patients	2/13	OR = 4.81 (95% CI = 0.955 - 24.24), Trend for less NBO	0.06 †

- Two tailed t test, † Fisher's exact test

Table 15.9 Outcome criteria for poisoned individuals who were treated < 12 hours, comparing treatment groups

Criterion	HBO Treatment Less than 12 Hours (n=31)	NBO Treatment Less than 12 hours (n=12)	Odds Ratio (95% CI)	p value
Time to unrecordable ECO	181.5 minutes (133.4 – 229.7)	478.2 minutes (337.1 – 619.2)		<0.0001 *
Deaths	0/31	0/12		1.0 †
Normal outcome	27/31	11/12	0.61 (0.06 to 6.13)	1.0 †
Persistent Neurological Sequelae	4/31	1/12	1.63 (0.16 to 16.28)	1.0 †
Delayed Neurological Sequelae	0/31	3/12	0.13 (0.005 to 3.55)	0.3 †
Return to previous occupation	30/31	12/12	0.81 (0.03 to 21.37)	1.00 †
Ongoing Psychiatric Morbidity	11/31	2/12	2.75 (0.51 to 14.9)	0.29 †

* Two tailed t test, † Fisher's exact test

Time to eliminate CO from breath

Despite experiencing more severe poisoning, the hyperbaric oxygen treated group demonstrated shorter treatment times to reach unrecordable ECO (the limit of resolution of the CO offgassing apparatus), than the NBO group. This result was also significant when the two treatments were compared for patients who received treatment within 12 hours of their CO poisoning.

Outcomes of Death, PNS, or DNS

There was no statistically significant difference in the risk of developing PNS or death when comparing the two methods of treatment, and no difference in individuals' ability to return to their previous occupation. No significant difference was detected when the groups were split into treatment < 12H or > 12H after CO poisoning.

A statistically significant increase in the number of patients developing DNS after treatment with NBO was noted. Although numbers in the series were small, the NBO group had three out of 13 patients relapsing, compared with 1 out 45 patients who were treated with HBO ($p=0.03$). This association with treatment method was not significantly different for the sub-group of patients who received treatment within 12 hours of their CO poisoning.

A trend was noted for patients receiving HBO treatment to have more ongoing psychiatric morbidity than those treated with NBO ($p=0.06$). This morbidity included depression, ongoing suicidal ideation, and psychosis. This was expected, because there were greater numbers of patients with a previous psychiatric history in the HBO group, they were more likely to be suicidal, and consume alcohol or drugs in association with their suicide attempt. It was not significantly different for the group of patients who received treatment within 12 hours of their CO poisoning, probably due to less suicidal patients being in the ≤ 12 H group.

15.4. Discussion

Entry variables that influenced outcome

In this study, very few of the entry criteria demonstrated statistically significant association with outcome. The patient's sex, smoking status and ingestion of drugs or alcohol, were not significantly associated with outcome. Increased age was not a risk factor for poor outcome, although there was an insignificant trend for DNS to occur in older patients.

Where recorded (often as estimates), the duration of exposure to CO was not significantly associated with outcome. Loss of consciousness at any stage, duration of loss of consciousness and conscious state or neurological rank in the ED did not correlate with final outcome. The fairly broad 4-point scale used to rank patient neurological status may have prevented subtle abnormalities from being detected that might have influenced outcome.

In this prospective series of patients, the finding of acidosis (pH<7.32) correlated with poor outcome. Weaver et al (2002) found that acidosis was associated with a worse outcome if patients were treated with NBO, compared to treatment with HBO. Gorman et al (1992) found no relationship between metabolic acidosis and outcome in their series. Scheinkestel et al (1999) reported acidosis in their series, however did not independently relate this to outcome. Acidosis probably reflects significant tissue hypoxia, and the risk of permanent neurological injury.

In this series, the recorded COHb and ECO breathing air or oxygen at study entry did not correlate with the outcomes PNS and DNS. There were large variations in time study entry, and substantial delays before patients received ECO measurements at Fremantle hospital ED. These delays were likely to have influenced the amount of ECO measured at the time of study entry. Samples for COHb and ECO were not taken at the rescue scene, and it is not possible to quantify the effect of prehospital and referring hospital oxygen treatment. Other studies that have attempted to correlate COHb with long-term outcomes have not demonstrated a significant relationship: Mathieu et al (1985), Goulon et al (1986), Norkool and Kirkpatrick (1985), Gorman et al (1992), Thom et al (1995). None of these studies recorded the time that the COHb was measured relative to the time of rescue from poisoning.

In some cases at the time of rescue, brain injury may be established, due to hypoxia or hypotension rather than direct neurological CO toxicity. In these circumstances patients would have more limited capacity for recovery, independent of their ECO or COHb levels (see figure 5.1). This may act as a

confounding influence on the link between body CO load in the ED, and neurological outcome. The finding of significantly greater numbers with acidosis in the poor outcome group supports this. Acidosis is an indicator of tissue hypoxia, and possibly a marker of permanent injury.

Precise oxygen treatment duration was not known for the time period prior to study entry. Initial CO loads were been reduced by this oxygen treatment. This limitation in study methodology also impacted upon any potential correlation between the initial ECO measurements and neuropsychological outcome. The main limitation was the delay in referral from other Perth Hospitals to Fremantle Hospital. To test the utility of ECO as a predictor of outcome, ECO samples would need to be taken from patients at the time they are rescued, in the prehospital setting. There was no significant association between time to zero CO and outcome.

Effect of delays to study entry and treatment

Delays in entry to the study, delays in oxygen treatment, and delays in receiving HBO treatment were also associated with a greater chance of poor outcome, particularly PNS. When their treatment was delayed greater than 12 hours, the group assigned to HBO had a highly significant chance of poor outcome. Only ten out of 49 patients received their allocated HBO treatment in less than 6 hours, and 32 out of 49 allocated to received their treatment in less than 12 hours. This meant that many of the patients had considerable delays before they reached Fremantle hospital, and hence their ECO levels were significantly affected by the treatment received prior to arrival at Fremantle Hospital. It may also have reflected referral bias, because only more severely affected individuals were referred from other centres. In the patients with low ECO values, it was not possible to extrapolate backwards to the time of their initial ED presentation to obtain an acute ECO estimate. A number of factors were likely to have adversely affected the accuracy of the extrapolation:

(1) The precise duration of oxygen administration was not known. All had periods on and off oxygen that were not recorded prior to their arrival at Fremantle Hospital.

(2) Oxygen concentrations during prehospital treatment were not known, only flow rates. Delivered oxygen concentration would have been influenced by mask fit and patient RMV.

(3) As was shown in chapter 13 of this study, there was a considerable variation between individuals in their elimination half-lives. Any extrapolation would have been based on an estimate of mean value.

(4) Use of low levels of CO (< 10 ppm), that were inside control ranges, may have introduced further inaccuracies

Very few studies have reported the time to oxygen treatment. Most studies report time to study entry and there is considerable variation between studies. It is likely that this factor is a significant confounder when attempting to delineate factors that influence outcome. Goulon et al (1986) are the only group to specifically compare outcomes for patients treated < 6 hours and > 6 hours. They found that mortality was 13.5% if HBO was administered less than 6 hours after poisoning, and 30.1% if administered greater than 6 hours after poisoning. They also found that the incidence of neurological sequelae was reduced if HBO was administered in less than 6 hours. Our findings for PNS are consistent with Goulon's data.

In my study, delays may have resulted from any one or more of a number of steps, which were not examined individually:

(1) Delay between rescue and transfer to primary hospital.

(2) Delay in deciding to refer, from the initial treating hospital

(3) Referral from peripheral hospital to parent tertiary facility before Fremantle Hospital

(4) Delay in initiating ambulance transfer

(5) Delay in ambulance pick-up of patient

(6) Retrieval transport time to Fremantle Hospital

(7) Delay in assessment/processing via Fremantle Hospital ED

(8) Delay in transfer and entry to Hyperbaric Chamber.

Delays are not desirable, based on available evidence that clinical outcomes may be improved if HBO treatment is administered within six hours of poisoning. Implementing a process of direct referral to the hyperbaric facility, for patients satisfying criteria for HBO treatment, could eliminate steps 2 to 7 above. Step (3) is of particular concern, whereby patients identified with CO poisoning were referred from their district hospital to "parent" tertiary hospital, before transfer to Fremantle Hospital. During the study, doctors who received direction and advice from their nominated "parent" tertiary hospital staffed many of the district hospitals, and hence they transferred patients to that hospital first. The step

was eliminated, after this study, allowing district hospitals to refer direct to Fremantle Hospital. A positive outcome of the study was to identify and correct these delays by changing the system of referral.

Other comparative and randomized trials have attempted to minimise the effect of treatment delay by using specific entry criteria. Unfortunately there is considerable variation between studies, making the data difficult to compare consistently. The following entry criteria were used: Raphael et al (1989) < 12 hours, Ducasse et al 1995 <12 hours, Thom et al (1995) < 6 hours, Mathieu et al (1998) < 12 hours and Weaver et al (2002) < 24 hours. Scheinkestel et al (1999) had no specific entry criteria, however they reported that there were no differences in outcomes for the HBO and NBO groups treated within four hours of poisoning.

Patient self-reporting of symptoms correlated with outcomes

At follow-up interview, abnormal responses of patients to the FSQ and GHQ-12 correlated significantly with poor outcome. Questions in the FSQ sought information from the patient about their ability to function in day to day life, and possible CO related sequelae. The GHQ-12 was included in an attempt to identify ongoing psychological distress (Goldberg and Blackwell 1970, Pevalin 2000). The finding of higher levels of self-reported morbidity in association with abnormal study outcomes suggests that the sequelae of CO had a significant impact on patients' daily functioning. Given patients with poor outcomes were significantly more likely to have their exposure to CO from a suicide attempt, this finding is not surprising. Raphael et al (1989) did not formally assess outcome using neuropsychiatric screening, but noted a very high rate (33.8% - 43.2%) of neuropsychiatric sequelae, as reported by patients. Weaver et al (2002) patients reported difficulties with memory, and this was associated with objective cognitive dysfunction. My study also confirmed that self-reported symptoms had a significant association with adverse outcomes.

15.4.1. Entry features linked to specific outcomes DNS, PNS and deaths

Delayed neurological sequelae

There were difficulties when analysing DNS as a subset of outcomes, due to the small numbers in the group. There was no statistically significant relationship between any of the entry criteria, and risk of

developing DNS. Three out of the four patients with DNS had received NBO treatment. Patients who were treated with NBO had significantly greater risk of DNS. The risk of DNS was not related to delay in treatment, as all cases received NBO less than 6 hours. The HBO treated patient who developed DNS, received HBO 18 hours after poisoning. Three out of the four patients who developed DNS, fully recovered after further treatment with HBO. The fourth patient who did not recover had mildly abnormal neuropsychiatric testing, and was classified as PNS, for final outcome analysis. A non-significant trend was identified, for patients with DNS to be older than those who did not develop DNS. When patients receiving delayed treatment were excluded from analysis, there was no significant difference in the rate of DNS between the two treatment groups.

Smith and Brandon (1973) were the first to describe DNS, and over one third of their series experienced deterioration in their personalities and memory. Over 10 percent had major neurological injury. They correlated DNS with lower levels of consciousness at admission and advancing age. Late treatment and increasing age are known risk factors for developing DNS (Goulon et al 1969, Choi 1983, Min 1985, Gorman et al 1992, Mark 1992, Mathieu et al 1998, Weaver et al 2002). Min demonstrated that DNS more commonly occurred in older individuals, and those with longer periods of coma. Min (1985) noted that all cases of DNS were over 30 years of age. They did not treat all their cases with HBO. The incidence of DNS was 34% for patients aged over 60. Although DNS improved as time progressed, 40 percent remained abnormal, at 1 year (Min 1985). Myers was the first to describe HBO treatment of DNS, with 100 percent success (Myers et al 1985). Myers also noted a lower incidence of DNS for patients who were initially treated with HBO. My findings were consistent with Myers et al's study, in that there was a lower incidence of DNS in the HBO treated group, and when DNS was detected, most cases responded to treatment with HBO. Appendix 18.7 describes a classic case of DNS that was successfully treated with HBO during our study period. This patient was not entered into our study, as he presented three weeks after receiving treatment with NBO.

Persistent Neurological Sequelae and Deaths

Suicidal patients had significantly increased risk of poor outcomes (PNS and death) after CO poisoning. This group was also more likely to have used a motor vehicle as a source of CO. There were trends for this group of patients to have delayed in study entry, and greater degree of neurological impairment in the ED. These findings were consistent with studies by Skopek and Perkins (1998), Routley (1998) and Scheinkestel et al (1999).

It was demonstrated in chapter 12 that suicidal patients were more likely to lose consciousness, and have a lower neurological rank in the ED. They also had higher ECO readings compared to other patients, despite greater delays to ED presentation. Furthermore, a high percentage of suicidal patients (54.5%) also consumed alcohol or drugs with their CO exposure. The intent of their poisoning is the likely reason for increased severity of poisoning in this group of patients. Suicidal individuals were likely to seek to avoid detection, taking longer to be treated after their poisoning, and they received a higher CO dose from longer exposures. It was demonstrated that they were also more likely to use automobiles with leaded petrol. Leaded petrol exhaust produces more CO than unleaded fuel (Routley 1998). Ingestion of drugs or alcohol may have led to longer exposures and exacerbated CO related hypoxia, due to depressive effects on respiration. The significantly greater risk of acidosis in these individuals is consistent with more severe exposures. All of these factors, in addition to ongoing psychiatric morbidity would contribute to the increased risk of PNS or death in the suicidal individuals.

Treatment method and outcomes

The study was not randomized, and patients were allocated into treatment groups based on clinical severity, hence comparison of treatment outcomes is not strictly valid. The HBO treated group was more likely to have a previous psychiatric history, have attempted suicide and consumed alcohol or drugs with their CO exposure. The HBO group had more severe exposures, with more frequent loss of consciousness, lower neurological rankings, lower MMSE scores, greater degree of acidosis and higher COHb levels. The reason for undertaking this detailed analysis was to assist with hypothesis generation concerning any unexpected observations in the treatment groups.

Two findings were not consistent with the outcomes expected from the study protocol:

(1) HBO treated patients had shorter times to zero ECO, despite have more severe poisoning and higher initial CO loads, as measured by COHb.

(2) HBO treated patients had lower risk of DNS.

The first finding explained by the shorter elimination half-life demonstrated for HBO. In chapter 13, CO elimination half-lives in HBO were 37.2 minutes (ppm method) and 36.5 minutes ml/min method),

compared to 110.1 minutes (ppm method) and 144.6 minutes (ml/min method) for NBO. Initial COHb levels were significantly higher in the HBO treated group. Initial ECO levels in the HBO treated group were higher than the NBO group, but the difference was not significant. Failure to find statistical significance resulted from a subset of the HBO treated group who were referred very late, and had ECO levels less than 5 ppm breathing air.

The second finding of higher rate of DNS in the NBO treated group was unexpected, as previous studies have correlated DNS with more severe poisoning (Smith and Brandon 1973, Choi 1983, Min 1986). Myers et al (1985), and Gorman et al (1992) noted a reduction in DNS in their HBO treated groups compared with NBO. My study data is consistent with a potential treatment effect favouring HBO that is independent of removal of CO via the lung. Thom et al (1995) demonstrated a similar beneficial effect of HBO. The mechanism for this HBO effect has not been elucidated. It may be at a biochemical level, where HBO is able to reverse the toxic effects of CO in neural pathways that use CO as a second messenger. Another possibility is reversal of lipid peroxidation. These were discussed in the thesis literature review. Further research is required in this area, particularly in light of the consistent finding that DNS occurs more frequently in older individuals exposed to CO.

15.5. Conclusions

In this series of CO poisoned patients, poor outcomes were associated with suicide attempts, and use of a motor vehicle as source of CO, delays in entry to the study, acidosis, delays in oxygen and HBO treatment. Poor outcome was also associated with adverse symptoms reported by patients at their follow-up review. In this series no other factors were able to predict good outcomes at entry to the study. Measurements of ECO at study entry did not correlate with final neurological outcome. Delays of patient entry to the study confounded the ECO results, and further research is needed, measuring ECO levels as early as possible, preferably in the prehospital phase.

Trends were noted for lower neurological rank in the ED to be associated with poor outcomes, as well as concomitant use of drugs/alcohol with the CO exposure. These trends were not quite statistically significant. Acute ECO measurements breathing air or oxygen, did not have any statistically significant correlation with risk of PNS or death. In this series, patients who lost consciousness did not have a significantly worse outcome than those who remained conscious.

Consistent with the study protocol, individuals allocated to receive HBO had more severe exposures, with loss of consciousness, they had lower neurological rankings, lower entry MMSE scores, greater degree of acidosis and higher COHb levels. HBO treated individuals were also more likely to have a previous psychiatric history, have attempted suicide and consumed alcohol or drugs with their CO exposure.

The HBO treatment was associated with faster removal of CO, to an end-point of unrecordable ECO, due to the shorter elimination half-life in HBO. Hyperbaric oxygen treatment was also associated with reduced risk of DNS.

16. THESIS MAJOR FINDINGS AND CONCLUSIONS

Before summarizing the conclusions of this thesis, it is relevant to document some of the limitations of the research.

16.1. Limitations of the research

The apparatus used to measure ECO and CO offgassing was not compared with other devices capable of measuring CO in the breath. I made an assumption that the manufacturer's stated accuracy was correct, and that this would be maintained throughout the study period, provided the apparatus was calibrated and serviced in accordance with the manufacturer's recommended schedules. Individuals contributing control data for this research were convenience samples as described. No attempt was made to match the demographics or smoking habits with the broader population of Perth, WA.

COHb was measured by a spectrophotometric method, and this had greater degrees of error for values < 2%. It is possible that the ECO apparatus had greater sensitivity at low levels of CO than the "gold standard" applying at the time.

There were significant time delays between measurements of COHb and ECO. The magnitude of these was not anticipated when the research was proposed. The time delays originated from after-hours call-in travel times, transfer of patients between hospitals, and transfers within Fremantle Hospital. The time delays caused delays of up to 1 hour between COHb and ECO samples for the poisoned patients. They were receiving active treatment to remove CO during the delay between samples, and this may have artificially lowered ECO measurements. Because patients were receiving NBO treatment during all transfers, many patients had very low levels of ECO, by the time they arrived at Fremantle Hospital. Only 12 "very acute" patients were studied. This did not allow sufficient samples to draw firm conclusions when comparing the elimination half-lives of ECO and COHb. In addition, the two-point method of measurement of COHb elimination half-life had limitations. Final post-treatment values of zero COHb could not be analysed by two-point method. Low numbers of very acute cases may also have affected the data when ECO was assessed as a diagnostic tool for CO poisoning. Greater numbers of acute cases may have improved the sensitivity and specificity of the ECO test.

The prospective case series was not randomized, and hence comparison of treatment outcomes (HBO vs NBO) was not strictly valid, and it is not possible to make firm conclusions regarding the usefulness of unrecordable ECO as a treatment end-point. Prior discussion with ethics committee members indicated that there would be significant resistance to a randomized study, because it was established practice to treat all severely poisoned patients with HBO at Fremantle Hospital since 1989. It was considered to be a significant alteration of normal practice to randomise severely poisoned patients into a treatment group using NBO. At the time of the study, there was only one randomized study of HBO versus 100% oxygen at 1ATA, and in that study, all severely poisoned patients were treated with HBO (Raphael et al 1989). Hence, a randomized study was not attempted, and there were unequal numbers in the NBO and HBO treatment groups. Total numbers in the case series were limited by the time that I worked at Fremantle Hospital. I completed my contract at the end of January 1994, which meant that all enrolments had to be completed by mid October 1993, to allow for 3-month follow-up. Hence the numbers in the series reflect all consecutive cases between April 1992, and October 1993. Larger numbers in case series may have resulted in significant results for trends, particularly among sub-groups.

There would be advantages to further investigating some parts of this research, using co-oximetry for COHb measurements. Ideally this would study heavy smokers allowing better time matching of samples, for COHb, air, NBO and HBO ECO values, to more precisely define the relationship between ECO and COHb, and also to calculate elimination half-lives in air using ECO technology.

Finally, the precise biochemical mechanisms causing tissue toxicity from CO remain unresolved. If these effects originate from a secondary process (not directly from CO), this may interfere with any attempts to establish a direct link between acute measurement of CO and the clinical outcomes from poisoning. Despite the above limitations, a number of conclusions can be made from the investigations undertaken in this research, and these are detailed in the following pages:

16.2. Conclusions

(1) A low cost, portable apparatus was successfully developed for measurement of ECO, O_2 concentration and minute volume. The apparatus was suitable for measurement of ECO in a variety of clinical settings with patients inhaling dry air or oxygen. Monitoring of O_2 concentration in real-time ensured that the stated dose of oxygen was delivered.

(2) Baseline levels of ECO are low in healthy non-smoking volunteers, and in non-smoking divers treated for decompression illness.

(3) Smokers have higher baseline ECO than non-smokers. ECO levels in smokers correlated positively with the number of cigarettes smoked per day, and negatively with the time since last cigarette. It was not possible to demonstrate a significant correlation between the cigarette CO content and the ECO.

(4) CO elimination from smokers was consistent with a single-phase exponential process.

(5) Expired CO increased as a function of increased P_IO_2 for smokers and diver controls.

(6) Under hyperbaric conditions at 2.8 ATA, CO offgassing in divers increased by a factor of 2.85. This resulted from greater volumes excreted, when the exhaled gas was depressurised. There was no significant increase in mean ECO concentration when breathing HBO compared to NBO.

(7) In a clinical series of 66 CO poisoned patients, there was a high percentage of males, a high percentage of individuals exposed themselves to CO as an act of deliberate self-harm, and a high percentage lost consciousness. Duration of LOC correlated significantly with the severity of neurological impairment observed for patients at presentation in the ED.

(8) There is a strong positive linear relationship between the ECO and COHb. This was observed for smoker controls and poisoned patients as well as the pooled data. The gradients and ratios for the ECO (ppm) versus COHb (%) for smokers and poisoned patients were consistent with data from Bedfont, but less that the values determined by Wallace (1998).

(9) Available data also suggest that the ECO reading may be more sensitive in detecting CO than the biochemical test for COHb. Expired CO was detectable in all non-smokers, however COHb could be detected using the biochemical test in only a minority of non-smokers.

(10) The linear relationship between ECO and COHb was confirmed for poisoned individuals, when breathing air, NBO and HBO. Elevating the P_IO_2 caused the ECO, and hence CO elimination to increase. There was no significant difference in the ECO in HBO at 2.8ATA, compared with NBO, however HBO caused a significant increase in the volume of CO excreted after it was depressurised to 1ATA.

(11) Breathing NBO and HBO, expired CO levels remained significant, when COHb became unrecordable. This suggests that a poisoned individual may have significant body stores of CO, at the time COHb may be unrecordable. It also suggests that a longer period of oxygen treatment may be required to reduce ECO to zero, than would occur if COHb were the marker of acute poisoning.

(12) The data indicate that measurement of ECO may potentially be more useful than COHb as a marker of acute treatment endpoint, because of greater sensitivity.

(13) Expired CO and COHb proved equally efficacious in identifying acutely poisoned individuals. Critical values of ECO >40 ppm or COHb > 7% were shown to be highly specific for CO poisoning. Expired CO levels greater than 40 ppm were 100% specific and 100% sensitive in identifying severe CO poisoning with acute cognitive impairment.

(14) In the range of ECO = 8 – 40 ppm, clinical information is required to separate the less severely poisoned patient from the smoker. This information should be available, because all poisoned individuals with ECO <40 ppm were able to cooperate with cognitive testing.

(15) Expired CO > 40ppm and COHb ≥ 15% had equal sensitivity and specificity in discriminating between severely poisoned and less severely poisoned patients.

(16) In the case series of 66 patients, individuals with LOC had longer exposures to the CO source than those without LOC, but did not have significantly higher ECO or COHb levels. Individuals with deliberate exposures were more likely to suffer LOC, had higher COHb and ECO levels than accidental exposures, and worse neurological ranks assessed in the ED.

(17) Individuals with deliberate exposure to CO were more likely to use automobiles with leaded petrol (hence higher [CO] in the exhaust) and ingest other medication and alcohol, than those with accidental poisoning. There was no significant difference in exposure duration when comparing deliberate versus accidental exposures.

(18) ECO and COHb measurements had a similar relationship to acute neurological CO toxicity. Higher levels of ECO and COHb positively correlated with more severe poisoning.

(19) The one-phase exponential model provided the best fit to the data in 98% of the curves from HBO treatment, and 96% of the curves from treatment with NBO. This finding supports the use of half-lives as an appropriate method to describe CO elimination.

(20) Measured ECO elimination half-lives were 110.1 and 144.6 minutes in NBO, and 37.2 and 36.5 minutes in HBO at 2.8 ATA.

(21) There was a seven to ten-fold variation of CO elimination between individuals, and this may have implications for the treatment of victims of poisoning.

(22) Age and smoking status did not appear to influence elimination of CO via the lungs in this sample of poisoned patients.

(23) Comparison of COHb and ECO elimination half-lives demonstrated a trend towards a shorter elimination half-life for COHb, which was significant in the NBO treatment group. This provided evidence that CO elimination via the lungs may be a more sensitive indicator of body stores of CO than COHb elimination. The finding of longer elimination half-lives using ECO measurements, also suggests that longer NBO and HBO treatment may be required than has been the normal practice of 6 to 12 hours NBO or a single HBO treatment documented in previous studies. The non-invasive technique of measuring ECO offers the possibility of tailoring of treatment to each individual's unique elimination kinetics.

(24) The clinical series demonstrated that treatment of acute CO poisoning to an end-point of unrecordable ECO correlated well with acute clinical improvement of the patient, when measured by improvement in neurological rank.

(25) The case series provided evidence that adverse neurological outcomes at 3 months were predicted by the neurological status of the patient at the specified treatment end-point when ECO was unrecordable.

(26) Normal neuropsychological status at unrecordable ECO did not predict patients who developed DNS. This indicated that close follow-up of normal patients, using cognitive function screening is still required in the first 4 – 6 weeks after treatment.

(27) In the series of CO poisoned patients, poor outcomes were associated with suicide attempts, use of a motor vehicle as source of CO, delays in entry to the study, acidosis, delays in oxygen and HBO treatment.

(28) Poor outcome was also associated with adverse symptoms reported by patients at their follow-up review.

(29) Measurements of ECO at study entry did not correlate with final neurological outcome. Delays of patient entry to the study confounded the ECO results, and further research is needed, measuring ECO levels as early as possible, preferably in the prehospital phase.

(30) In this series, patients who lost consciousness did not have a significantly worse outcome than those who remained conscious.

(31) Consistent with the study protocol, individuals allocated to receive HBO had more severe exposures, with loss of consciousness, had lower neurological rankings, lower entry MMSE scores, greater degree of acidosis and higher COHb levels. HBO treated individuals were also more likely to have a previous psychiatric history, have attempted suicide and consumed alcohol or drugs with their CO exposure.

(32) HBO treatment was associated with faster removal of CO, to an end-point of unrecordable ECO, due to the shorter elimination half-life in HBO. Hyperbaric oxygen treatment was also associated with reduced risk of DNS.

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18. APPENDICES

APPENDIX 18.1 DETAILS OF STUDY POPULATION AT ENTRY

APPENDIX 18.2 COGNITIVE TESTS

APPENDIX 18.3 FUNCTIONAL STATUS QUESTIONNAIRE (FSQ)

APPENDIX 18.4 GENERAL HEALTH QUESTIONNAIRE (GHQ-12)

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APPENDIX 18.8 RESEARCH SUBMISSION, CONSENT FORMS AND ETHICS APPROVAL

APPENDIX 18.9 PRESENTATIONS AND PUBLICATIONS FROM THIS RESEARCH

APPENDIX 18.1
Table 18.1 DETAILS OF STUDY POPULATION AT ENTRY (N=66)

Subject and Number	Age	Status in Study	Aetiology of CO	Acute CO Effect	ED Clinical grade	Delay to Treatment	Initial Treatment	Neuro Status at Zero ECO	Outcome (neuropsychological tests)
Male K204	23	Refused to participate	Leaded car exhaust (DSH)	No LOC	4	130 minutes	100% Oxygen	Unknown	Not formally tested, returned to work at 3 months
Male J421	25	Refused to participate	Unknown (DSH)	No LOC	3	90 minutes	100% Oxygen	Unknown	Not known
Male x999	35	Refused to participate	Unleaded car exhaust (DSH)	LOC 120 minutes	Unknown	60 minutes	100% Oxygen	Unknown	Not formally tested, returned to work at 3 months
Male J724	76	Late entry, Had DNS	LPG fridge in caravan, Accidental	LOC 720 minutes	2	120 minutes	100% Oxygen	Unknown	DNS - Treated HBO at 3 weeks. Recovered - minor defect (PNS)
Male E727	30	Late entry lost at follow-up	Leaded car exhaust (DSH)	LOC 120 minutes	3	26.5 hours	100% Oxygen HBO at 37 hours	Normal	No formal follow-up, returned to work 3 months, no symptoms
Male E050	41	Entered, lost at follow-up	Leaded car exhaust (DSH)	Unknown LOC	2	150 minutes	100% Oxygen HBO at 9 hours	Normal	Follow-up to one month normal, returned to work phoned, no symptoms
Male C211	20	Late Entry and DEATH	Leaded car exhaust (DSH)	LOC 240 minutes	1	60 minutes	100% Oxygen HBO at 12¼ hours	Severe PNS	Death - primary cause CO
Female K551	6	Late Entry and DEATH	Leaded car exhaust Homicide/suicide	LOC 180 minutes	1	60 minutes	100% Oxygen HBO at 28 hours	Severe PNS	Death due to infarct right cerebral hemisphere - lacerated carotid artery
Poor Outcomes									
Male K434	24	Late Entry	Leaded car exhaust (DSH)	LOC > 12 hours	2	2880 minutes	100% Oxygen HBO at 53 hours	Severe PNS	Severe PNS, Incontinent, bed bound
Male C024	29	Late Entry	Leaded car exhaust (DSH)	LOC 5 minutes	3	1200 minutes	100% Oxygen HBO at 36 Hours	Mild PNS	Moderate PNS, Drug use and heavy alcohol use
Male L529	20	Late Entry	Leaded car exhaust (DSH)	Unknown LOC	2	1080 minutes	100% Oxygen HBO at 60 hours	Moderate PNS	Moderate PNS, Korsakov's syndrome
Male L530	22	Late Entry	Unleaded car exhaust (DSH)	LOC 360 Minutes	2	48 hours	100% Oxygen HBO at 50 hours	Moderate PNS	Moderate PNS, memory defects, returned to basic work 3 Months

Table 18.1 continued. Poor Outcomes

Subject (age) and Number	Age	Status in Study	Aetiology of CO	Acute CO Effect	ED Clinical grade	Delay to Treatment	Initial Treatment	Neuro Status at Zero ECO	Outcome (neuropsychological tests)
Male A029	59	Late Entry	Unleaded car exhaust (DSH)	LOC 10 minutes	4	90 minutes	100% Oxygen HBO at 15 Hours	Mild PNS	Further deteriorated 2 days post treatment, treated HBO. Mild PNS at 3 months
Male F043	35	Entry < 12 hours	Leaded car exhaust (DSH)	LOC 20 Minutes	3	90 minutes	100% Oxygen HBO at 11 hours	Mild PNS	Mild PNS at 1 month, returned to work, continued depression 3 months
Male G541	23	Entry < 12 hours	Leaded car exhaust (DSH)	Unknown if LOC	3	150 minutes	100% Oxygen HBO at 3 hours	Moderate PNS	Mild PNS at 1 month, Normal at 3 months, returned to work
Male J723	27	Entry < 12 hours	Unleaded car exhaust (DSH)	Unknown if LOC	2	120 minutes	100% Oxygen HBO at 7.5 hours	Mild PNS	Mild PNS at 1 month, recovered & returned to work by 3 months
Female K613	22	Entry < 12 hours	Leaded car exhaust (DSH)	LOC 180 Minutes	2	60 minutes	100% Oxygen HBO at 10.5 hours	Mild PNS	Mild PNS, Ongoing psychosis, at 3 months, not returned to usual work
Male K220	46	Entry < 12 hours	Leaded car exhaust (DSH)	No LOC	4	120 minutes	100% Oxygen	Mild PNS	Mild PNS at 1 month, returned to work by 3 months
Female L540	13	Late Entry	Other car exhaust Accidental	No LOC	4	2160 minutes	100% Oxygen	Mild PNS	Mild PNS, Recovered at 3 months, returned to school
Male K013	42	Late Entry	Leaded car exhaust (DSH)	No LOC	3	400 minutes	100% Oxygen HBO at 18 hours	Normal	Worsened with DNS, treated HBO Returned to work by 3 months but impaired cognitive. Mild PNS
Male C434	30	Entry < 12 hours	Leaded car exhaust Work Accident	No LOC	4	180 minutes	100% Oxygen	Normal	DNS at 1 month treated with HBO. Normal at 3 months, returned to usual work
Female H040	27	Entry < 12 hours	Unleaded car exhaust Accidental	No LOC	4	330 minutes	100% Oxygen	Borderline	DNS 1 month, treated with HBO, normal at 3 months
Male L220	40	Entry < 12 hours	Leaded car exhaust Work Accident	No LOC	4	90 minutes	100% Oxygen	Normal	DNS 1 month, treated with HBO. OK at 3 months, returned to work

Table 18.1 continued. Good Outcomes

Subject (age) and Number	Age	Status in Study	Aetiology of CO	Acute CO Effect	ED Clinical grade	Delay to Treatment	Initial Treatment	Neuro Status at Zero ECO	Outcome (neuropsychological tests)
Male A034	44	Entry < 12 hours	Leaded car exhaust (DSH)	LOC 40 minutes	2	90 minutes	100% Oxygen HBO at 4 hours	Normal	Normal at 1 and 3 months
Male B072	24	Entry < 12 hours	Unleaded car exhaust (DSH)	LOC 255 minutes	2	15 minutes	100% oxygen HBO at 4 hours	Normal	Normal at 1 and 3 months, never worked before or after poisoning
Male B318	7	Entry < 12 hours	Inside kettle BBQ Accidental	LOC 5 minutes	3	120 minutes	100% oxygen HBO at 6.5 hours	Normal	Normal at 1 month, continued successful schooling, same grade
Male C072	28	Late Entry	Unknown (DSH)	LOC 5 minutes	3	120 minutes	100% Oxygen HBO at 39 hours	Normal	Normal at 3 months, returned to work
Male C717	23	Late Entry	Unleaded car exhaust (DSH)	LOC 300 minutes	4	720 minutes	100% Oxygen HBO at 24 hours	Normal	Normal at 3 months but not returned to work
Male C726	30	Late Entry	Diesel car exhaust (DSH)	LOC 120 minutes	4	420 minutes	100% Oxygen HBO at 30 hours	Normal	Normal at 3 months and returned to work
Male D042	30	Entry < 12 hours	Unleaded car exhaust (DSH)	No LOC	2	90 minutes	100% Oxygen HBO at 8.5 hours	Normal	Normal at 3 months and returned to work
Male D062	29	Entry < 12 hours	Leaded car exhaust (DSH)	LOC 240 minutes	1	45 minutes	100% Oxygen HBO at 4 hours	Normal	Normal at 3 months and returned to work
Male D423	26	Entry < 12 hours	Leaded car exhaust (DSH)	LOC 180 Minutes	1	40 minutes	100%Oxygen HBO at 3.5 hours	Normal	Normal at 3 months and returned to work
Male D428	26	Entry < 12 hours	Leaded car exhaust (DSH)	LOC 100 Minutes	2	120 minutes	100% Oxygen HBO at 4.25 hours	Normal	Normal at 3 months and returned to work
Male D712	41	Entry < 12 hours	Leaded car exhaust (DSH)	LOC 20 Minutes	1	20 minutes	100% Oxygen HBO at 4.5 hours	Normal	Normal at 3 months and returned to work
Male E024	48	Entry < 12 hours	Leaded car exhaust (DSH)	LOC 15 Minutes	3	30 minutes	100% Oxygen HBO at 5.5 hours	Normal	Normal at 3 months and returned to work
Male E200	36	Entry < 12 hours	Leaded car exhaust (DSH)	LOC 120 Minutes	2	40 minutes	100% Oxygen HBO at 6.5 hours	Normal	Normal at 3 months and returned to work

Table 18.1 continued. Good outcomes

Subject (age) and Number	Age	Status in Study	Aetiology of CO	Acute CO Effect	ED Clinical grade	Delay to Treatment	Initial Treatment	Neuro Status at Zero ECO	Outcome (neuropsychological tests)
Female E316	9	Entry < 12 hours	Inside kettle BBQ Accidental	LOC 5 Minutes	3	120 minutes	100% Oxygen HBO at 6.5 hours	Normal	Normal at 3 months, continued successful schooling, same grade
Male F040	30	Entry < 12 hours	Leaded car exhaust (DSH)	LOC 5 Minutes	3	90 minutes	100% Oxygen HBO at 5.5 hours	Normal	Normal at 3 months, never worked before or after poisoning
Male G073	28	Late entry	Leaded car exhaust (DSH)	LOC 30 Minutes	2	10 minutes	100% Oxygen HBO at 24 hours	Normal	Normal at 3 months and returned to work
Male G202	26	Entry < 12 hours	Leaded car exhaust (DSH)	LOC 10 Minutes	3	60 minutes	100% Oxygen HBO at 4.5 hours	Normal	Normal at 3 months and returned to work
Male G425	42	Entry < 12 hours	Unleaded car exhaust (DSH)	LOC 180 Minutes	3	75 minutes	100% Oxygen HBO at 5.25 hours	Normal	Normal at 3 months and returned to work
Female G432	20	Late Entry	Leaded car exhaust (DSH)	No LOC	2	240 minutes	100% Oxygen HBO at 14 hours	Normal	Normal at 3 months, not returned to work
Male G533	23	Late Entry	Leaded car exhaust (DSH)	LOC 90 Minutes	3	60 minutes	100% Oxygen HBO at 15 hours	Normal	Normal at 3 months, never worked before or after poisoning
Male G535	16	Entry < 12 hours	Unleaded car exhaust (DSH)	LOC 30 Minutes	3	150 minutes	100% Oxygen HBO at 6 hours	Normal	Normal at 3 months and returned to work
Female G543	12	Entry < 12 hours	Inside kettle BBQ Accidental	LOC 15 Minutes	4	120 minutes	100% Oxygen HBO at 6.5 hours	Normal	Normal at 3 months continued successful schooling, same grade
Female G714	19	Late Entry	Unleaded car exhaust (DSH)	No LOC	3	60 minutes	100% Oxygen HBO at 8 hours	Normal	Normal at 3 months and returned to work
Male H072	41	Entry < 12 hours	Unleaded car exhaust (DSH)	LOC 120 Minutes	2	120 minutes	100% Oxygen HBO at 7.5 hours	Normal	Normal at 3 months, returned to work
Male H315	11	Entry < 12 hours	Inside kettle BBQ Accidental	No LOC	3	120 minutes	100% Oxygen HBO at 6.5 hours	Normal	Normal at 3 months continued successful schooling, same grade
Female H557	9	Entry < 12 hours	Inside kettle BBQ Accidental	LOC 15 Minutes	3	60 minutes	100% Oxygen HBO at 8 hours	Normal	Normal at 3 months continued successful schooling, same grade
Male J056	38	Entry < 12 hours	Inside kettle BBQ Accidental	No LOC	4	120 minutes	100% Oxygen HBO at 6.5 hours	Normal	Normal at 3 months and returned to work
Female J220	25	Entry < 12 hours	Inside kettle BBQ Accidental	LOC 4 Minutes	3	120 minutes	100% Oxygen HBO at 6.5 hours	Normal	Normal at 3 months and returned to work

Table 18.1 continued. Good outcomes

Subject (age) and Number	Age	Status in Study	Aetiology of CO	Acute CO Effect	ED Clinical grade	Delay to Treatment	Initial Treatment	Neuro Status at Zero ECO	Outcome (neuropsychological tests)
Female J221	42	Entry < 12 hours	Inside kettle BBQ Accidental	LOC 2 Minutes	4	270 minutes	100% Oxygen HBO at 10.5 hours	Normal	Normal at 3 months and returned to work
Male J221	14	Entry < 12 hours	Inside kettle BBQ Accidental	No LOC	3	270 minutes	100% Oxygen HBO at 10.5 hours	Normal	Normal at 3 months continued successful schooling, same grade
Male K069	30	Entry < 12 hours	Inside kettle BBQ Accidental	No LOC	4	60 minutes	100% Oxygen HBO at 8 hours	Normal	Normal at 3 months and returned to work
Male K217	38	Entry < 12 hours	Leaded car exhaust (DSH)	LOC 450 Minutes	4	300 minutes	100% Oxygen HBO at 6 hours	Normal	Normal at 3 months and returned to work
Male K725	39	Entry < 12 hours	Leaded car exhaust (DSH)	LOC 15 Minutes	3	15 minutes	100% Oxygen HBO at 12 hours	Normal	Normal at 3 months and returned to work
Male L212	26	Entry < 12 hours	Unleaded car exhaust (DSH)	No LOC	4	60 minutes	100% Oxygen HBO at 10.5 hours	Normal	Normal at 3 months and returned to work
Male L432	26	Entry < 12 hours	Leaded car exhaust (DSH)	LOC 60 Minutes	3	120 minutes	100% Oxygen HBO at 12 hours	Normal	Normal at 3 months and returned to work
Male A070	26	Entry < 12 hours	Inside kettle BBQ Accidental	No LOC	4	480 minutes	100% Oxygen	Normal	Normal at 3 months and returned to work
Male C555	4	Entry < 12 hours	Inside kettle BBQ Accidental	No LOC	4	210 minutes	100% Oxygen	Normal	Normal at 3 months, continued normal development
Male C710	22	Entry < 12 hours	Leaded car exhaust (DSH)	No LOC	4	30 minutes	100% Oxygen	Normal	Normal at 3 months and returned to work
Female D314	40	Entry < 12 hours	Inside kettle BBQ Accidental	No LOC	4	480 minutes	100% Oxygen	Normal	Normal at 3 months and returned to work
Male H714	5	Entry < 12 hours	Unknown? Leaded exhaust Accidental	No LOC	4	90 minutes	100% Oxygen	Normal	Normal at 3 months, continued normal development
Female J221	8	Entry < 12 hours	Inside kettle BBQ Accidental	No LOC	3	210 minutes	100% Oxygen	Normal	Normal at 3 months, continued successful schooling, same grade
Female K322	35	Entry < 12 hours	Inside kettle BBQ Accidental	No LOC	4	60 minutes	100% Oxygen	Normal	Normal at 3 months and returned to work
Male K727	3	Entry < 12 hours	Unknown? Leaded exhaust Accidental	No LOC	4	90 minutes	100% Oxygen	Normal	Normal at 3 months, continued normal development

APPENDIX 18.2 COGNITIVE TESTS

The screening cognitive tests used in this study are found overleaf:

Glasgow Coma Score

Mini Mental State Examination

Symbol Digit Test

Digit Recall Test

APPENDIX 18.2.1 GLASGOW COMA SCORE

		SCORE	*TOTAL*
EYE RESPONSE	***Awake***	***4***	
	Open to Voice	***3***	
	Open to Pain	***2***	
	No Response	***1***	
		TOTAL EYE SCORE	
VERBAL RESPONSE	***Orientated***	***5***	
	Confused	***4***	
	Words Only	***3***	
	Sounds Only	***2***	
	No Response	***1***	
		TOTAL VERBAL SCORE	
MOTOR RESPONSE	***Obeys Commands***	***6***	
	Localises Pain	***5***	
	Withdraws to Pain	***4***	
	Flexes to Pain	***3***	
	Extends to Pain	***2***	
	No Response	***1***	
		TOTAL MOTOR SCORE	
		GLASGOW COMA SCORE OUT OF 15	

APPENDIX 18.2.2 MINI MENTAL STATE EXAMINATION (MMSE)

Fremantle Hospital Hyperbaric Medicine Unit

Mini Mental State Examination Sheet

Date:_____

Diagnosis:

Name:
Address:

Date of birth:
Sex:

Mental Function Test	Score
ORIENTATION Score one point for correct answers to each of the following questions: What is the Time? Day? Date? Month? Year?	5 points ( )
What is the name of this Ward? This Hospital? This State? This City? This Country?	5 points ( )
REGISTRATION Name three objects (viz. Car, dog, book). Score up to 3 points if, at the first attempt the patient repeats in order, the three objects you have named. Score 1 or 2 if this is the number of objects named. Endeavour, by further attempts and prompting, to have all three repeated, so as to test later.	3 points ( )
ATTENTION AND CALCULATION Ask the patient to subtract 7 from 100, and then 7 from the result. Repeat this 5 times, scoring 1 for each correct subtraction.	5 points ( )
RECALL Ask for the three objects repeated in the registration test, scoring 1 for each correctly recalled	3 points ( )
LANGUAGE Score 1 point for each of two objects (pencil, watch) correctly named	2 points ( )
Score 1 point if the following phrase is correctly repeated "No ifs, ands, or buts"	1 points ( )
Score 3 points if a three stage command is correctly executed, 1 for each stage. Eg "With the index finger of your right hand touch the tip of your nose and then your left ear"	3 points ( )
Point below to CLOSE YOUR EYES and ask the patient to do what is written. Score 1 point if the patient closes his eyes.	1 point ( )
Ask the patient to write a sentence on the back of this sheet. Score 1 point if the sentence is sensible and has a verb and a subject.	1 point ( )
Copy the diagram on the back of this sheet. Score 1 point if this is correctly copied.	1 point ( )
Total (/ 30)	( )

Level of consciousness 1_____10
Alert Drowsy Stupor Coma

Scoring: 23 or less denotes probable cognitive impairment (4.3% false positive: 76 % detection rate) and must be interpreted in the light of all other clinical data. Extremely poor orientation and registration may point to delirium.

CLOSE YOUR EYES

Write a Sentence below:

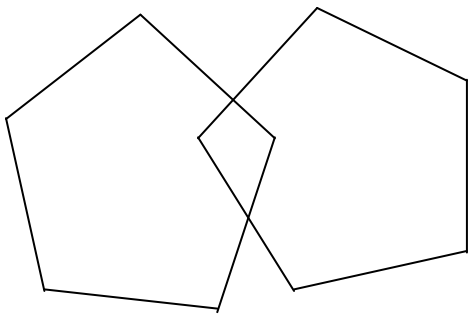
……

……

……

……

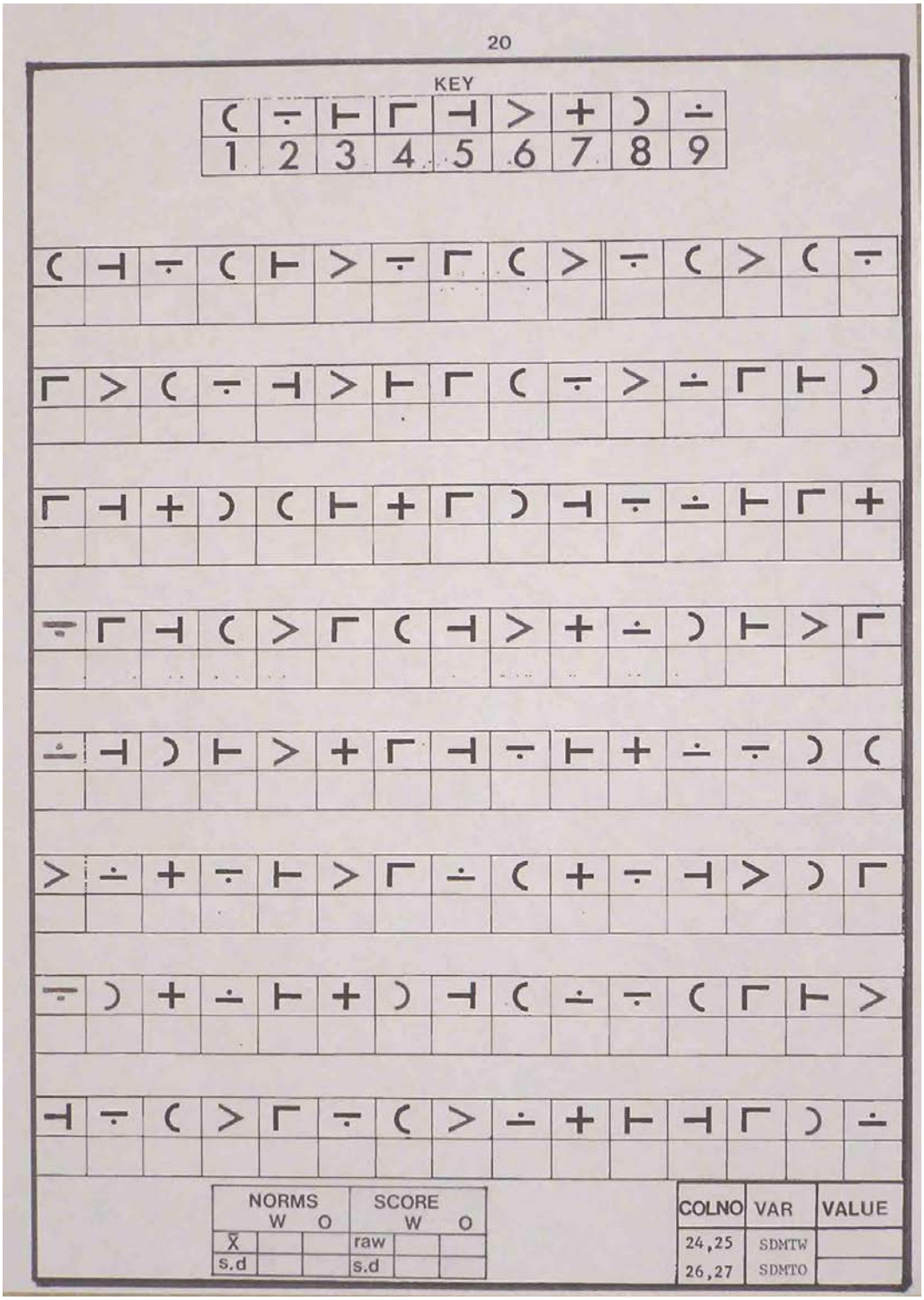
Copy the following diagram:



APPENDIX 18.2.3 DIGIT SPAN TEST (Forward and Reverse)

DIGIT SPAN Discontinue after failure on both trials of any item Administer BOTH TRIALS of each item, even if subject passes first trial			
DIGITS FORWARD		Pass/Fail	Score 2,1 or 0
1.	5 – 8 – 2		
	6 – 9 – 4		
2.	6 – 4 – 3 – 9		
	7 – 2 – 8 – 6		
3.	4 – 2 – 7 – 3 – 1		
	7 – 5 – 8 – 3 – 6		
4.	6 – 1 – 9 – 4 – 7 – 3		
	3 – 9 – 2 – 4 – 8 – 7		
5.	5 – 9 – 1 – 7 – 4 – 2 – 8		
	4 – 1 – 7 – 9 – 3 – 8 – 6		
6.	5 – 8 – 1 – 9 – 2 – 6 – 4 – 7		
	3 – 8 – 2 – 9 – 5 – 1 – 7 – 4		
7.	2 – 7 – 5 – 8 – 6 – 2 – 5 – 8 – 4		
	7 – 1 – 3 – 9 – 4 – 2 – 5 – 6 – 8		
Total Score Forwards			
DIGITS BACKWARD		Pass – Fail	Score 2,1 or 0
1.	2 – 4		
	5 – 8		
2.	6 – 2 – 9		
	4 – 1 – 5		
3.	3 – 2 – 7 – 9		
	4 – 9 – 6 – 8		
4.	1 – 5 – 2 – 8 – 6		
	6 – 1 – 8 – 4 – 3		
5.	5 – 3 – 9 – 4 – 1 – 8		
	7 – 2 – 4 – 8 – 5 – 6		
6.	8 – 1 – 2 – 9 – 3 – 6 – 5		
	4 – 7 – 3 – 9 – 1 – 2 – 8		
7.	9 – 4 – 3 – 7 – 6 – 2 – 5 – 8		
	7 – 2 – 8 – 1 – 9 – 6 – 5 – 3		
Total Score Backwards			
FORWARDS + BACKWARDS TOTAL (MAXIMUM = 28)			

APPENDIX 18.2.4 TIMED SYMBOL DIGIT TEST (TSDT)


20
KEY
1 2 3 4 5 6 7 8 9
NORMS W O
X̄
s.d
SCORE W O
raw
s.d
COLNO VAR VALUE
24,25 SDMTW
26,27 SDMTO

APPENDIX 18.3 FUNCTIONAL STATUS QUESTIONNAIRE (FSQ)

Follow-up Questionnaire

	Question	Answer Yes or No
1)	Do you feel completely well?	
(2)	Have you had problems with headaches?	
(3)	Have you experienced problems with memory?	
(4)	Do you note problems with concentration?	
(5)	Have you had problems with vision?	
(6)	Have you returned to your usual occupation?	
(7)	Are you driving a motor vehicle?	
(8)	Have you experienced mood or irritability problems?	

Score one point for each negative response

APPENDIX 18.4 GENERAL HEALTH QUESTIONNAIRE (GHQ-12)

Introduction " I would like to ask you a few questions about your thoughts and feelings over the past few weeks."

One point scored for each response reflecting negative emotions

HAVE YOU RECENTLY: (Yes/No)

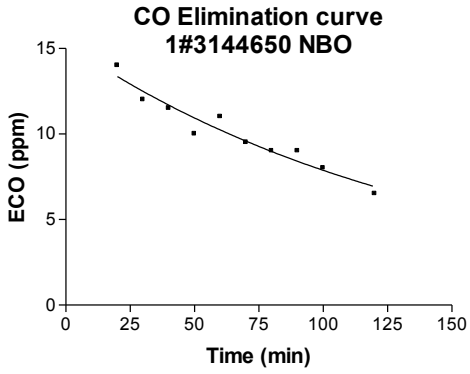
- **Been able to concentrate on whatever you are doing?**
- **Lost much sleep over worry?**
- **Felt that you are playing a useful part in things?**
- **Felt capable of making decisions about things?**
- **Felt constantly under strain?**
- **Felt that you could not overcome your difficulties?**
- **Been able to enjoy your normal day-to-day activities?**
- **Been able to face up to your problems?**
- **Been feeling unhappy and depressed?**
- **Been losing confidence in yourself?**
- **Been thinking of yourself as a worthless person?**
- **Been feeling reasonably happy, all things considered?**

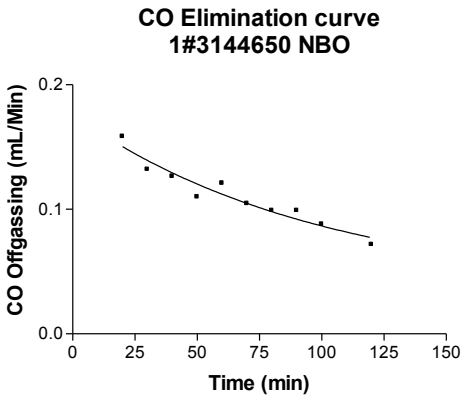
Reference: Goldberg and Williams 1988

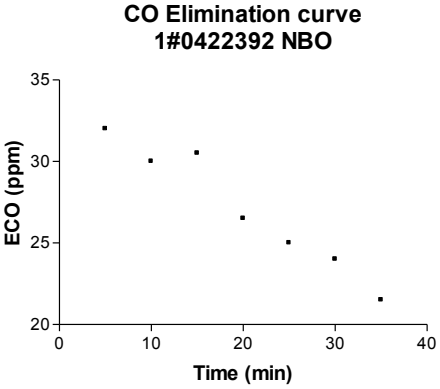
APPENDIX 18.5 DETAILED TESTING BY NEUROPSYCHOLOGISTS

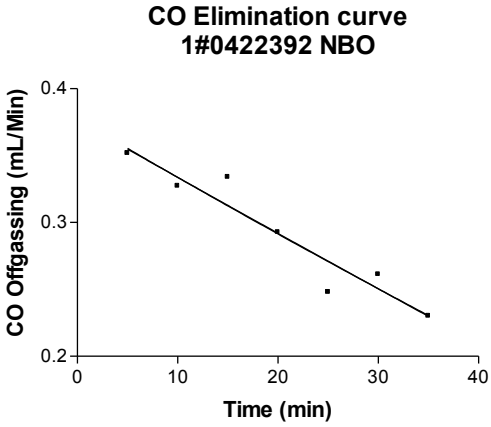
- **Wechsler Adult Intelligence Scale - Revised**
- **Untimed test of receptive language skills**
- **Immediate Memory Span - digits forward and backwards**
- **Verbal and Spatial Short term Memory**
- **Verbal and Spatial New Learning**
- **Verbal Fluency**
- **Timed Coding test**
- **Austin Maze Learning Test**
- **Grip strength, Dexterity and speed**
- **Sensory tests of finger agnosia and graphaesthesia**
- **Complex graphic figure - copied**

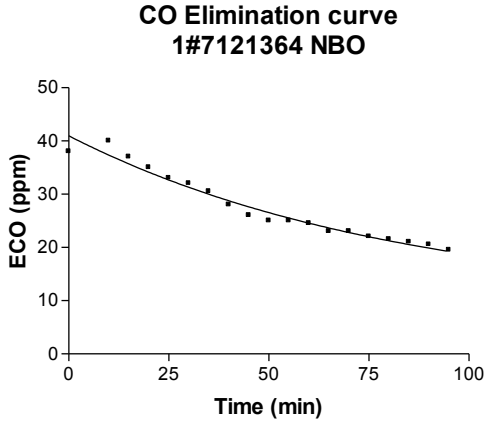
APPENDIX 18.6
DETAILED CO ELIMINATION CURVES FOR CHAPTER 13
NBO ELIMINATION CURVES

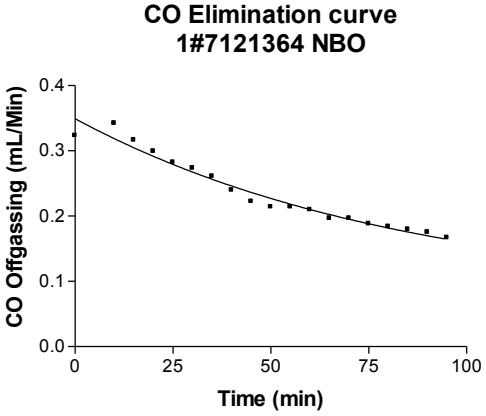


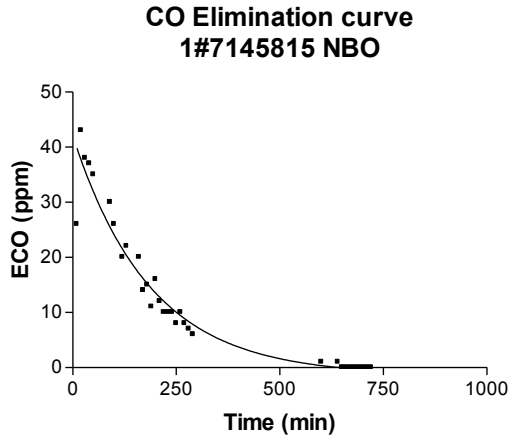








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ECO (ppm)
Time (min)
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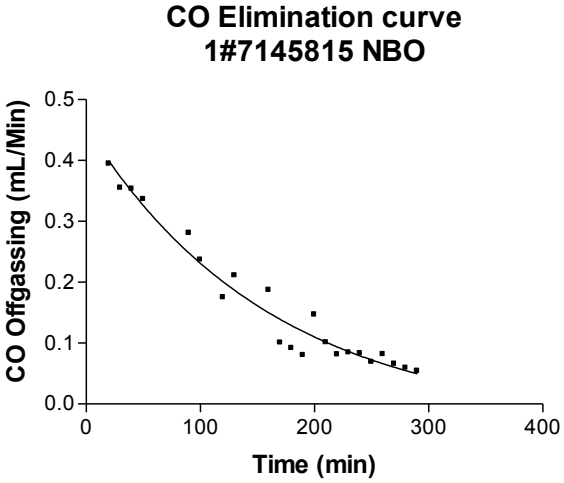
10
20
30
40
50
0
250
500
750
1000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CO Offgassing (mL/Min)
Time (min)
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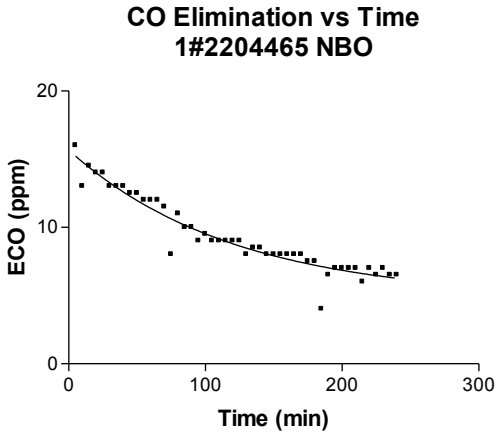
0.4
0.5
0
100
200
300
400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ECO (ppm)
Time (min)
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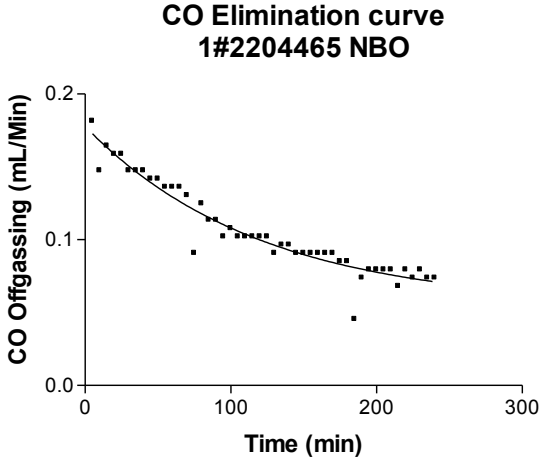
20
0
100
200
300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CO Offgassing (mL/Min)
Time (min)
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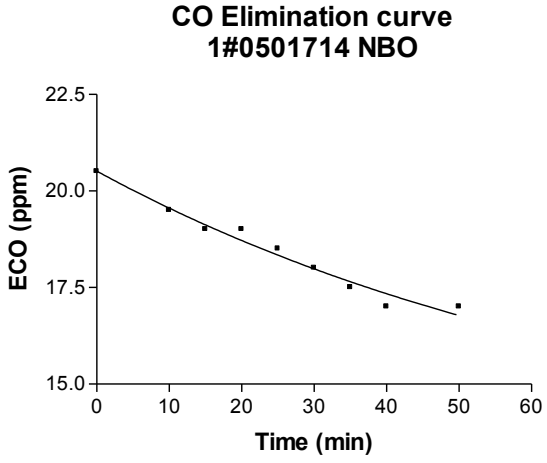
0.1
0.2
0
100
200
300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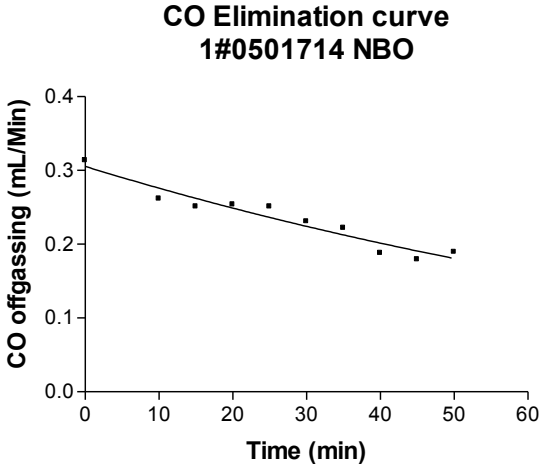
20.0
22.5
0
10
20
30
40
50
60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0.2
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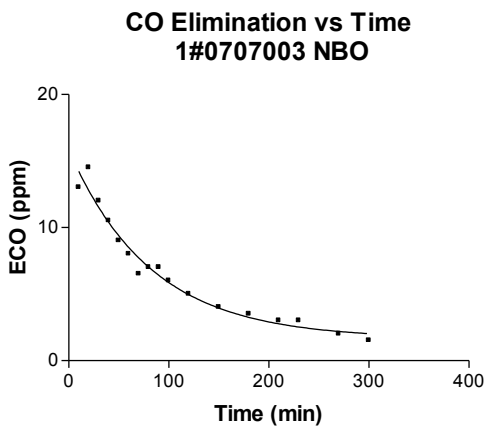
0.4
0
10
20
30
40
50
60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Time (min)
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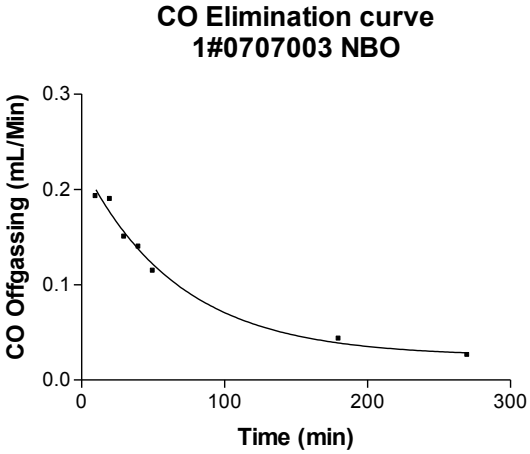
20
0
100
200
300
400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0.2
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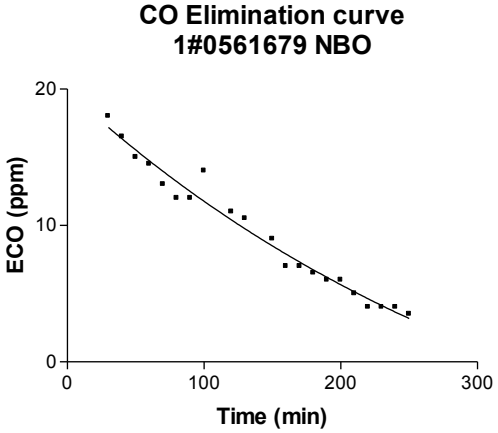
200
300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ECO (ppm)
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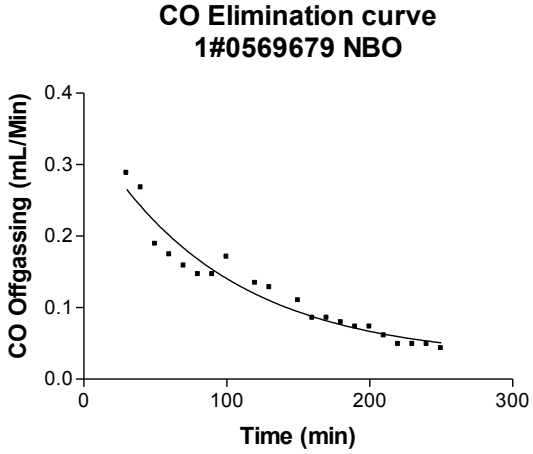
100
200
300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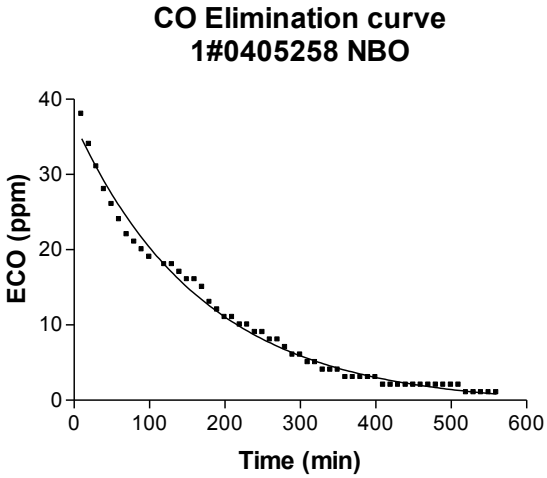
0
100
200
300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20
30
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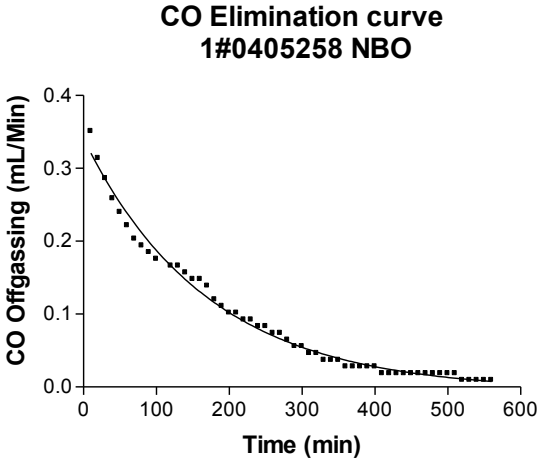
400
500
600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300
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500
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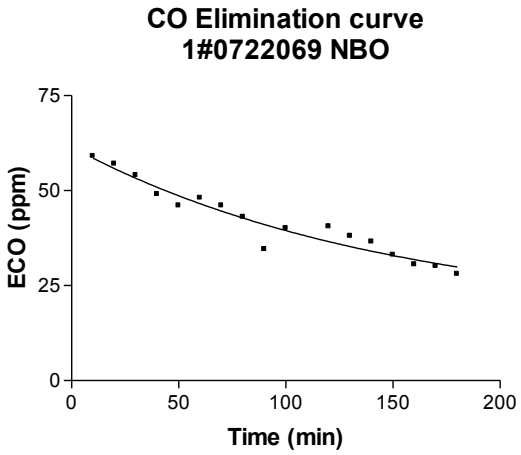
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Time (min)
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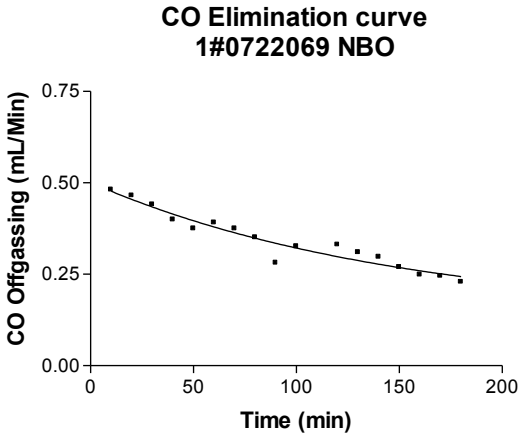
25
50
75
0
50
100
150
200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100
150
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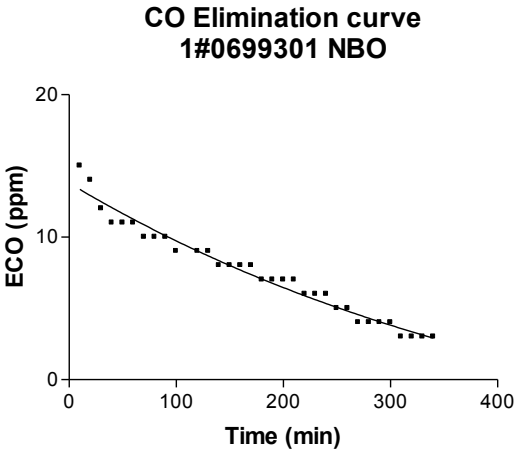
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Time (min)
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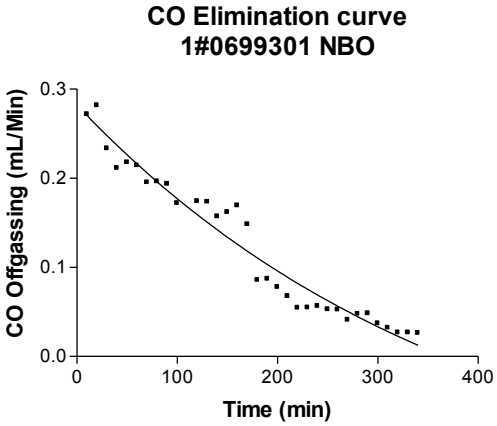
20
0
100
200
300
400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CO Offgassing (mL/Min)
Time (min)
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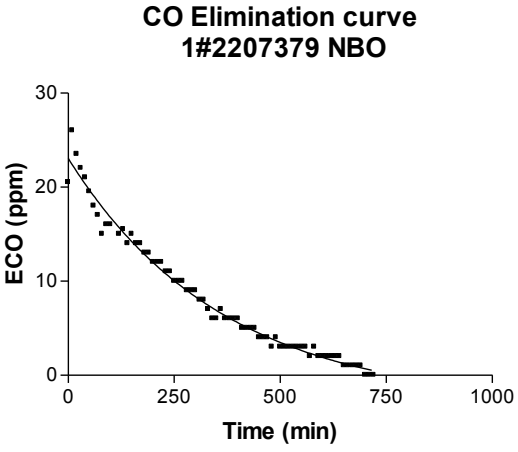
0.2
0.3
0
100
200
300
400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ECO (ppm)
Time (min)
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30
0
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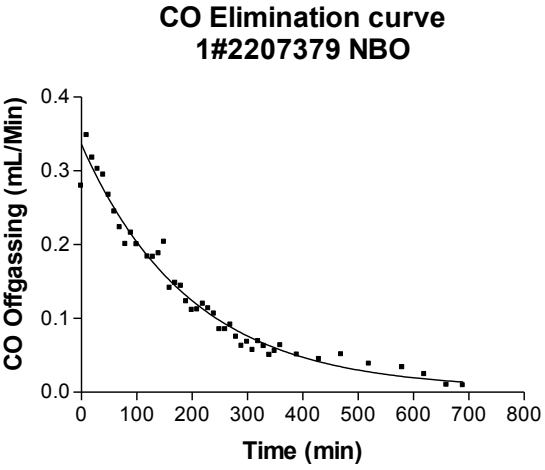
500
750
1000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CO Offgassing (mL/Min)
Time (min)
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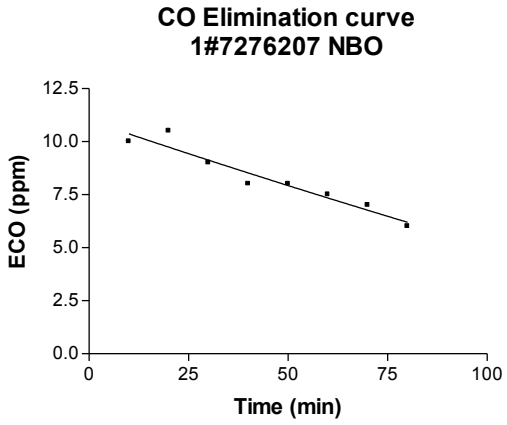
0.4
0
100
200
300
400
500
600
700
800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ECO (ppm)
Time (min)
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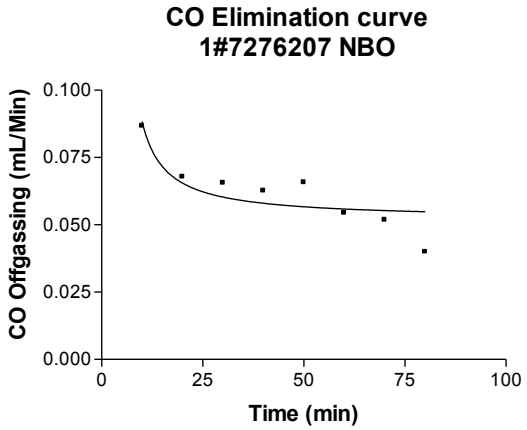
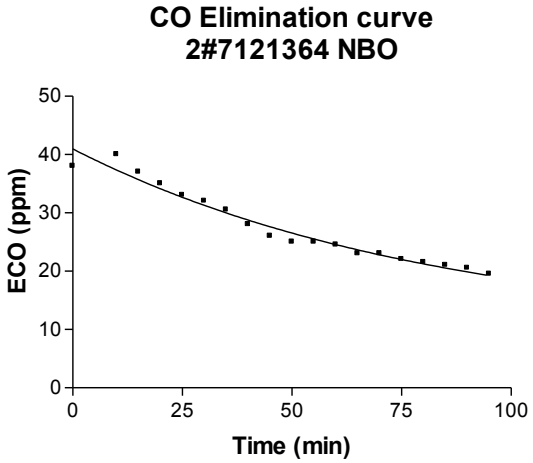
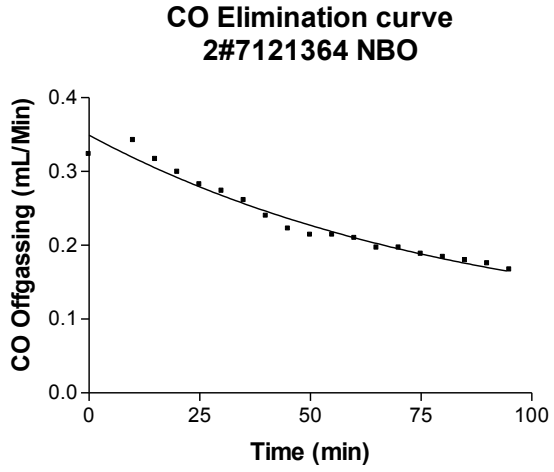
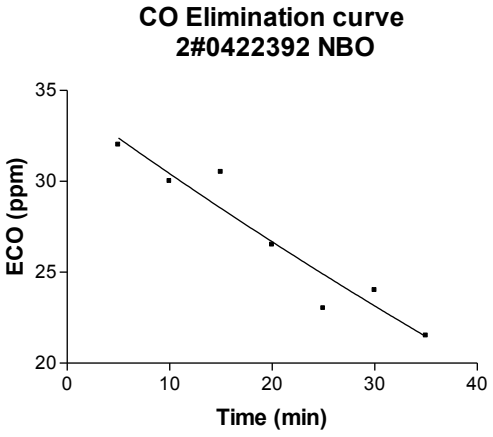
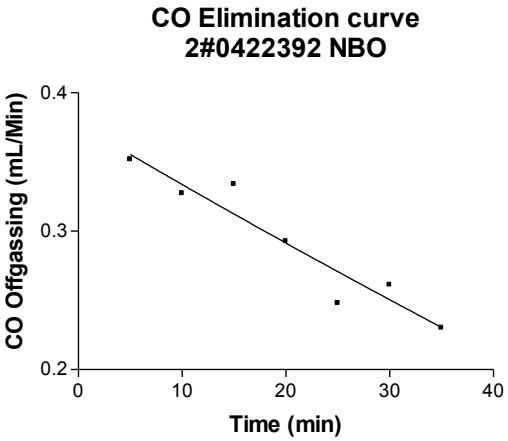
7.5
5.0
2.5
0.0
0
25
50
75
100

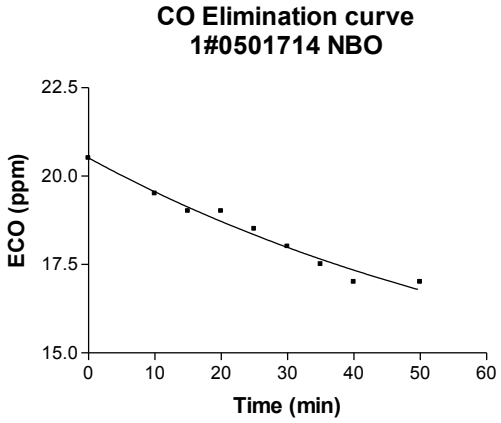

CO Elimination curve
1#7276207 NBO
CO Offgassing (mL/Min)
Time (min)
0.100
0.075
0.050
0.025
0.000
0
25
50
75
100

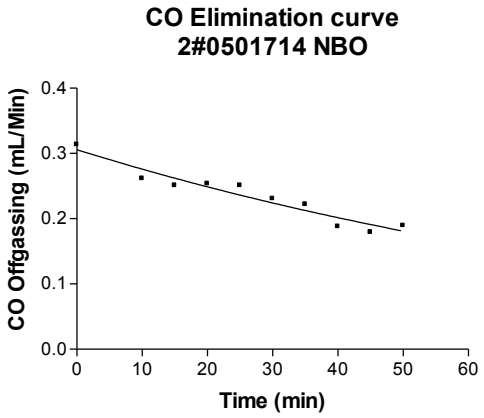

CO Elimination curve
2#7121364 NBO
ECO (ppm)
Time (min)
50
40
30
20
10
0
0
25
50
75
100

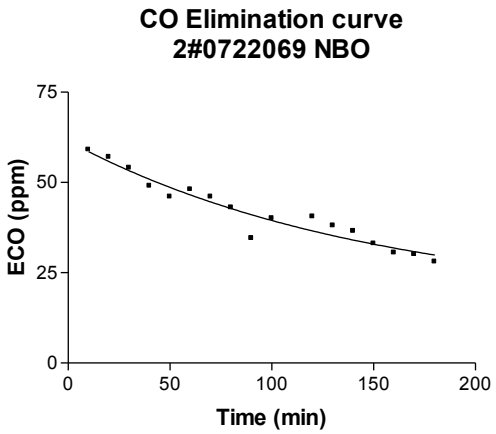

CO Elimination curve
2#7121364 NBO
CO Offgassing (mL/Min)
Time (min)
0.4
0.3
0.2
0.1
0.0
0
25
50
75
100

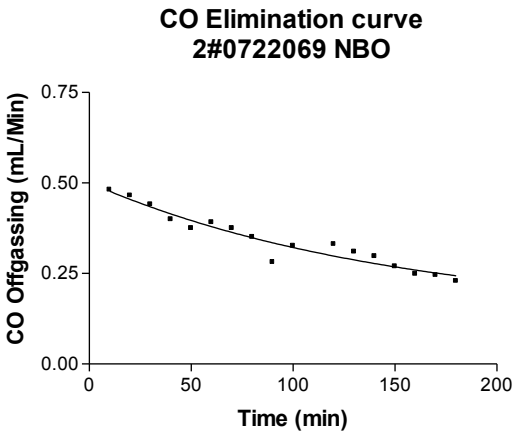

CO Elimination curve
2#0422392 NBO
ECO (ppm)
Time (min)
35
30
25
20
0
10
20
30
40

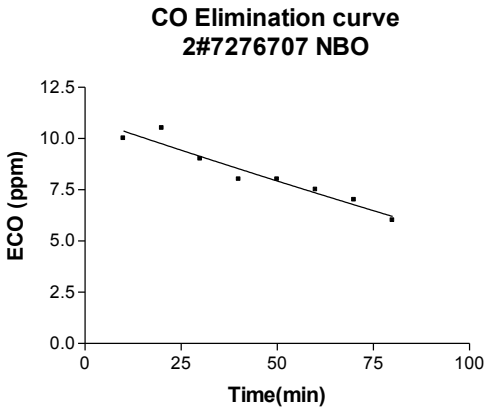

CO Elimination curve
2#0422392 NBO
CO Offgassing (mL/Min)
Time (min)
0.4
0.3
0.2
0
10
20
30
40

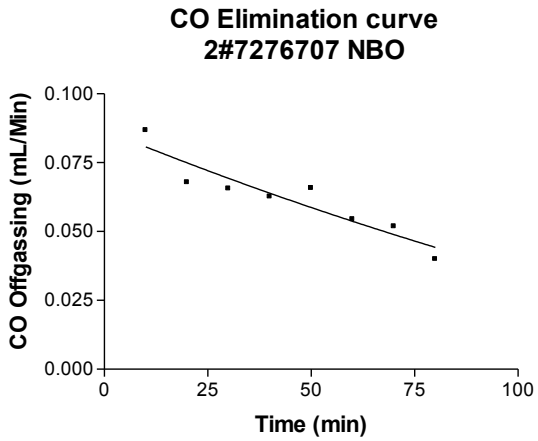

CO Elimination curve
1#0501714 NBO
ECO (ppm)
22.5
20.0
17.5
15.0
0
10
20
30
40
50
60
Time (min)


CO Elimination curve
2#0501714 NBO
CO Offgassing (mL/Min)
0.4
0.3
0.2
0.1
0.0
0
10
20
30
40
50
60
Time (min)

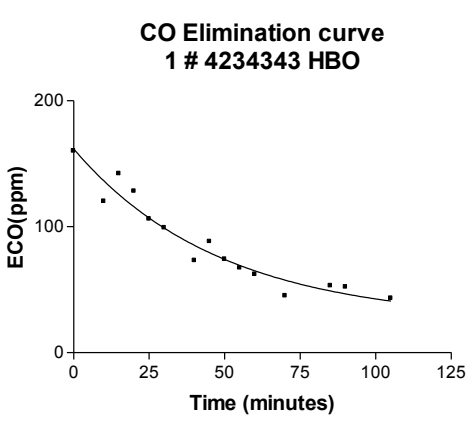

CO Elimination curve
2#0722069 NBO
ECO (ppm)
75
50
25
0
0
50
100
150
200
Time (min)

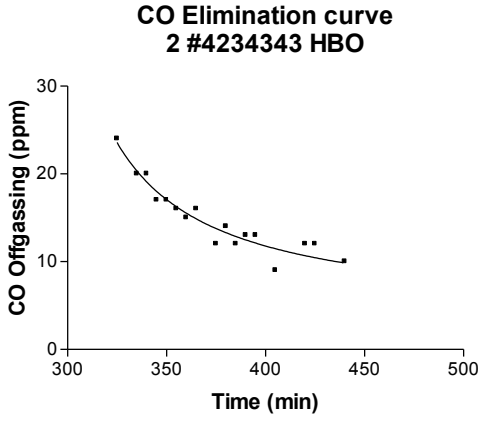

CO Elimination curve
2#0722069 NBO
CO Offgassing (mL/Min)
0.75
0.50
0.25
0.00
0
50
100
150
200
Time (min)

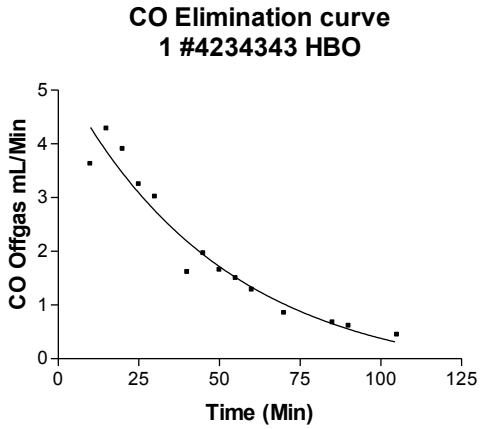

CO Elimination curve
2#7276707 NBO
ECO (ppm)
12.5
10.0
7.5
5.0
2.5
0.0
0
25
50
75
100
Time(min)

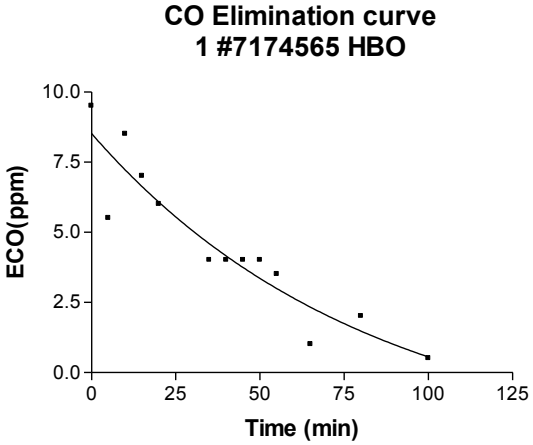

CO Elimination curve
2#7276707 NBO
CO Offgassing (mL/Min)
0.100
0.075
0.050
0.025
0.000
0
25
50
75
100
Time (min)

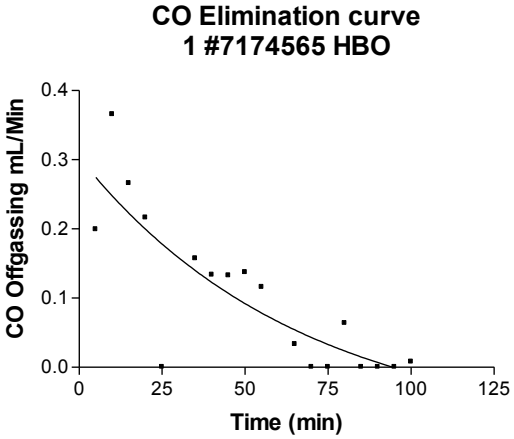
HBO ELIMINATION CURVES

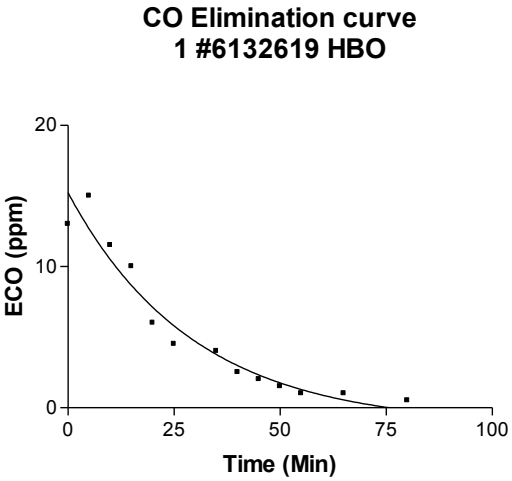


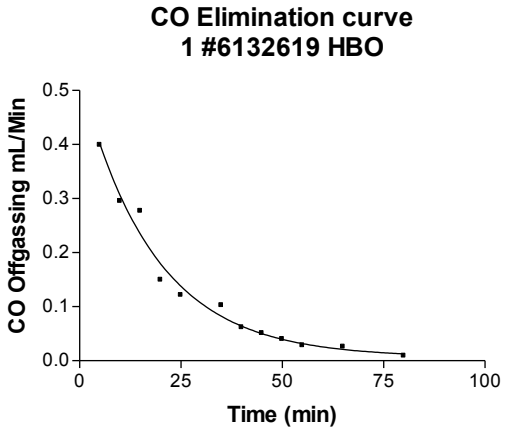


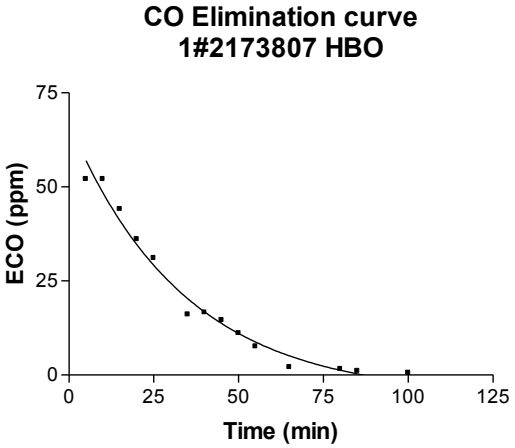


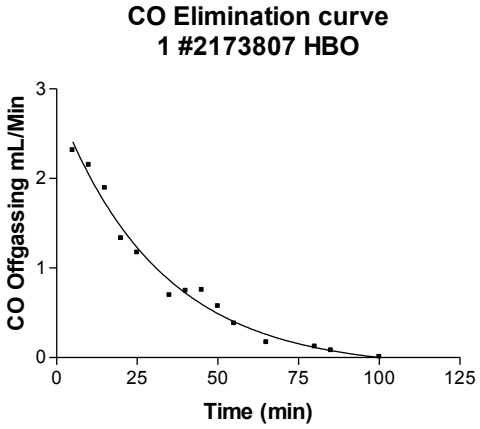


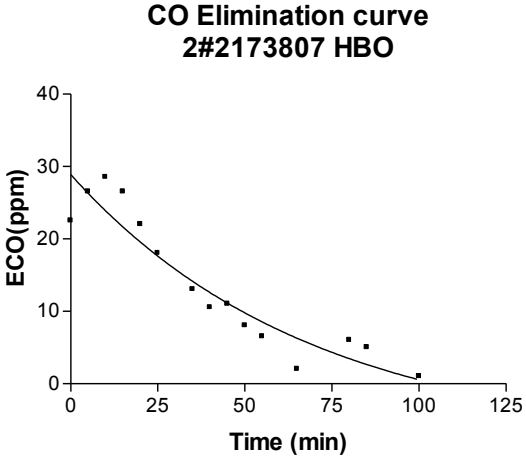


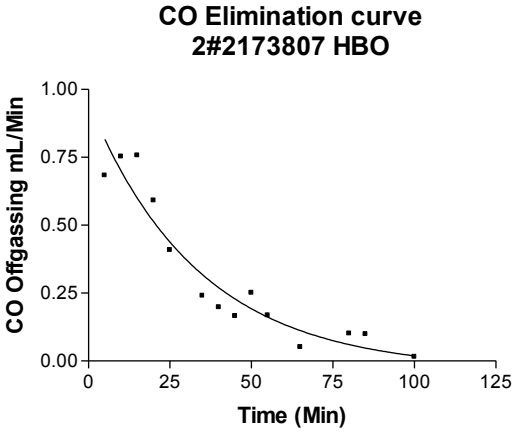


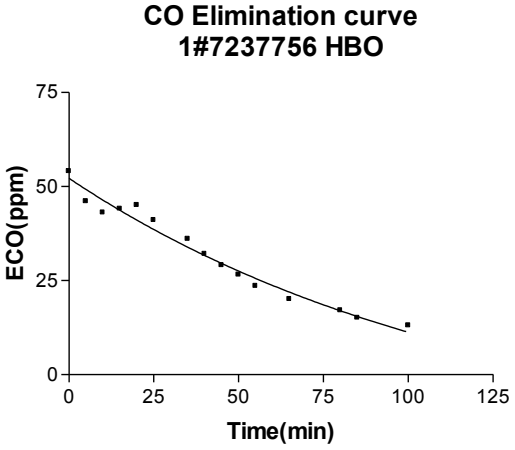

CO Elimination curve
1 #6132619 HBO
CO Offgassing mL/Min
0.5
0.4
0.3
0.2
0.1
0.0
0
25
50
75
100
Time (min)

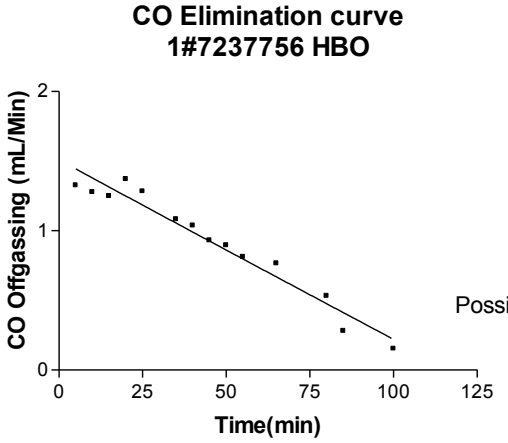

CO Elimination curve
1#2173807 HBO
ECO (ppm)
75
50
25
0
0
25
50
75
100
125
Time (min)


CO Elimination curve
1 #2173807 HBO
CO Offgassing mL/Min
3
2
1
0
0
25
50
75
100
125
Time (min)

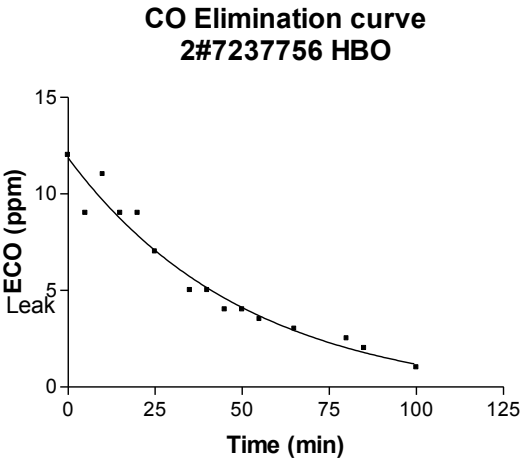

CO Elimination curve
2#2173807 HBO
ECO(ppm)
40
30
20
10
0
0
25
50
75
100
125
Time (min)

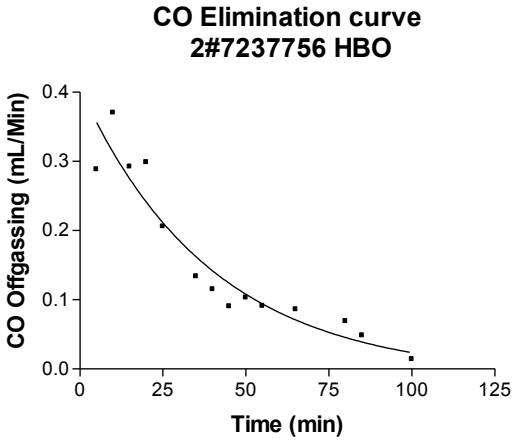

CO Elimination curve
2#2173807 HBO
CO Offgassing mL/Min
1.00
0.75
0.50
0.25
0.00
0
25
50
75
100
125
Time (Min)

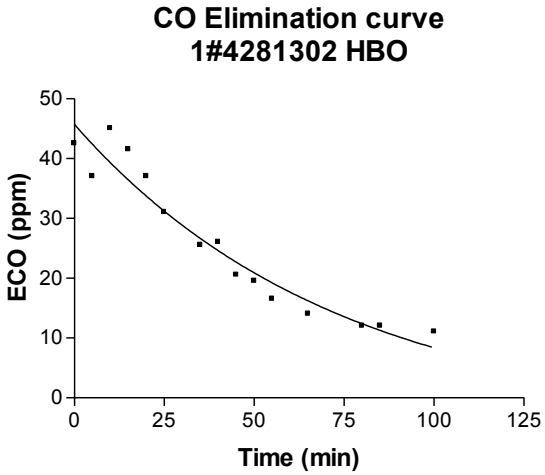

CO Elimination curve
1#7237756 HBO
ECO(ppm)
75
50
25
0
0
25
50
75
100
125
Time(min)

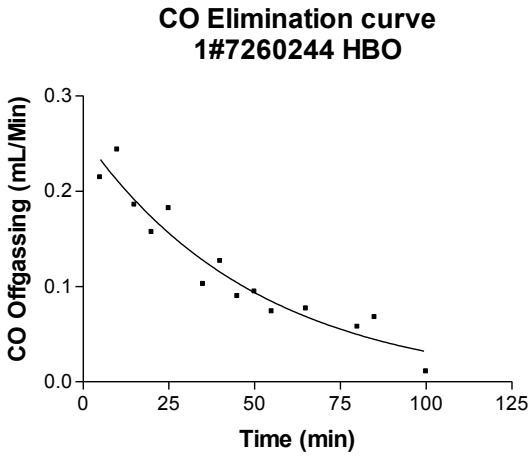


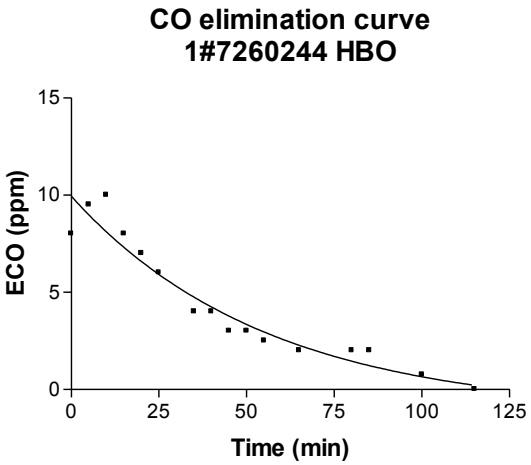
Possible Mask Leak

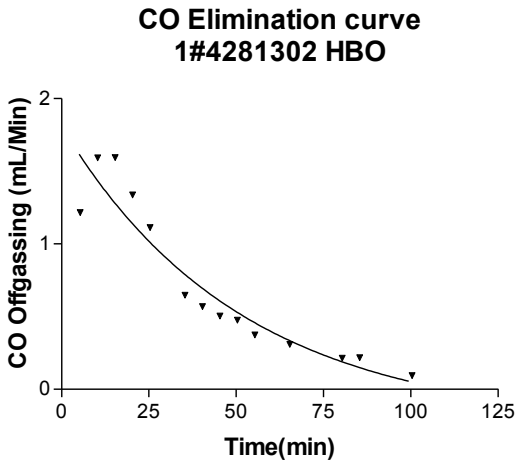


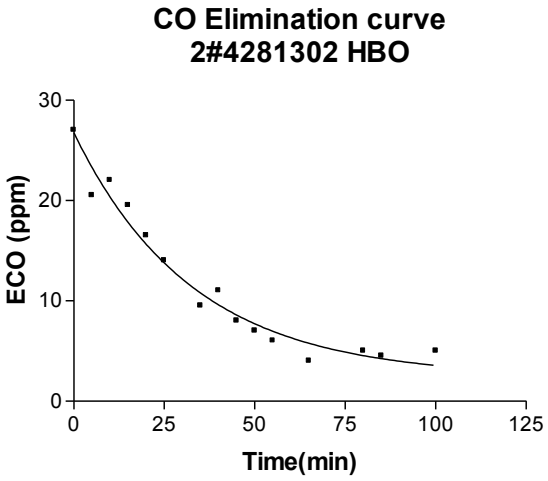


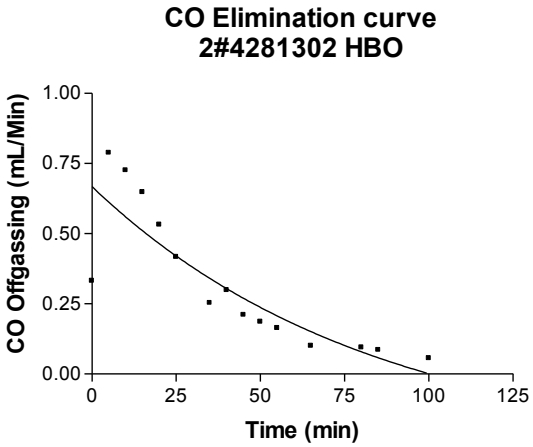


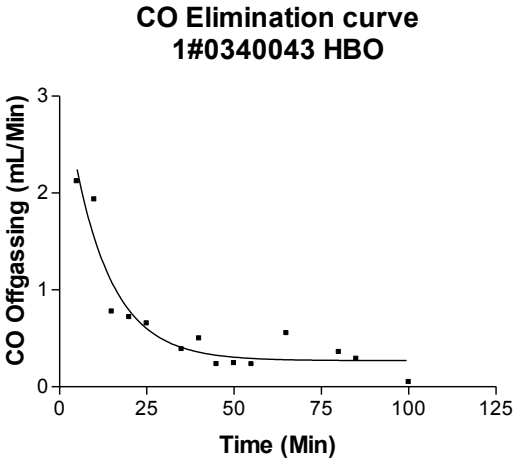


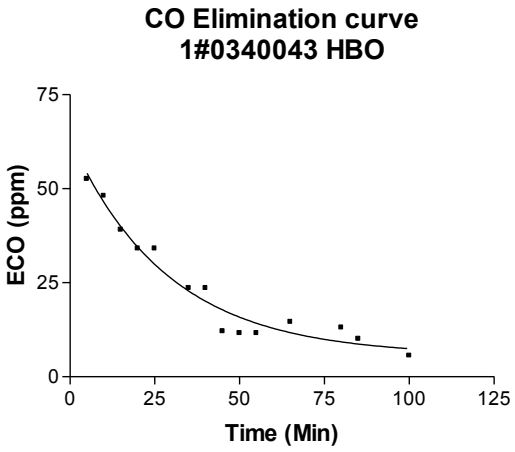


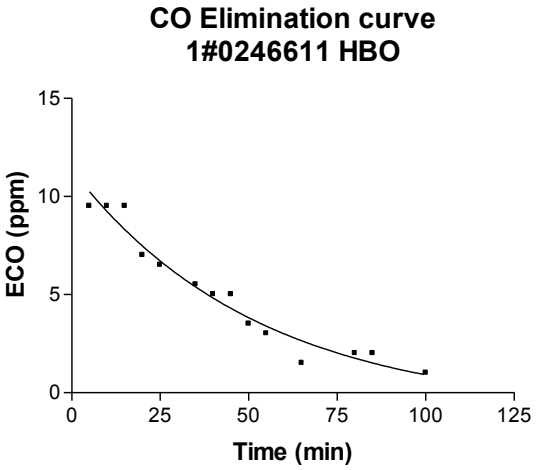

CO Elimination curve
1#4281302 HBO
CO Offgassing (mL/Min)
Time(min)

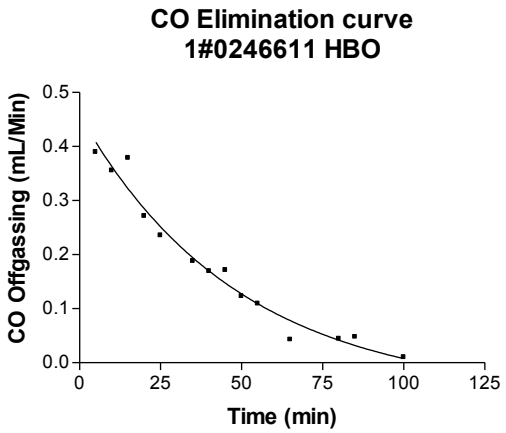

CO Elimination curve
2#4281302 HBO
ECO (ppm)
Time(min)

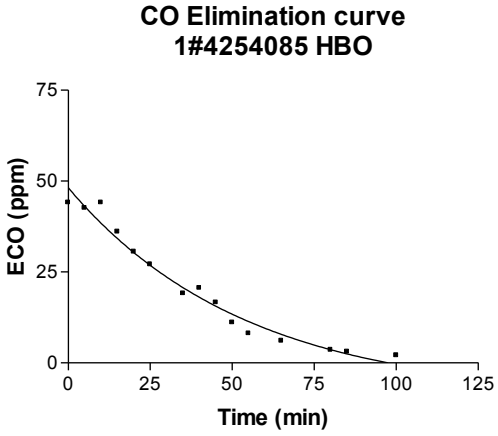

CO Elimination curve
2#4281302 HBO
CO Offgassing (mL/Min)
Time (min)

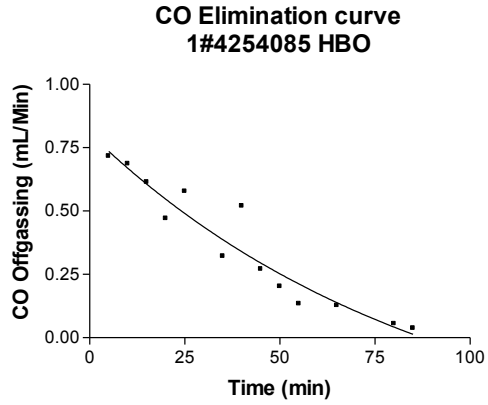

CO Elimination curve
1#0340043 HBO
CO Offgassing (mL/Min)
Time (Min)

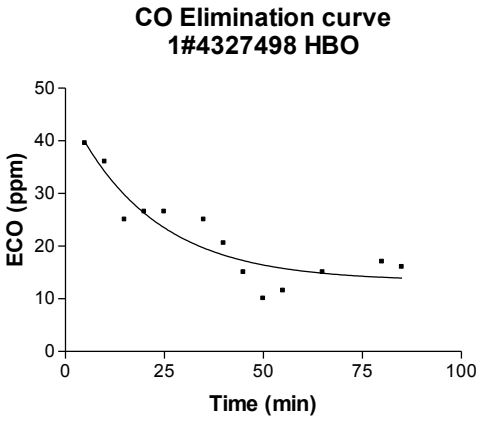

CO Elimination curve
1#0340043 HBO
ECO (ppm)
Time (Min)

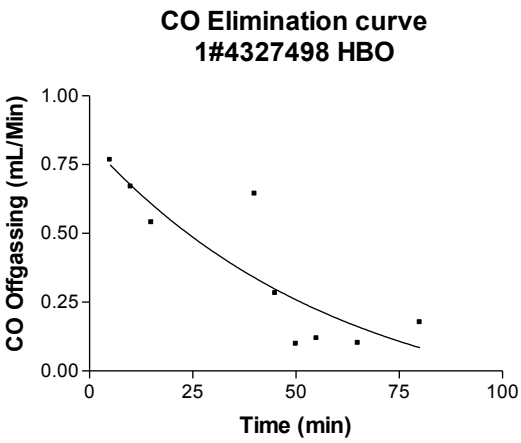

CO Elimination curve
1#0246611 HBO
ECO (ppm)
Time (min)

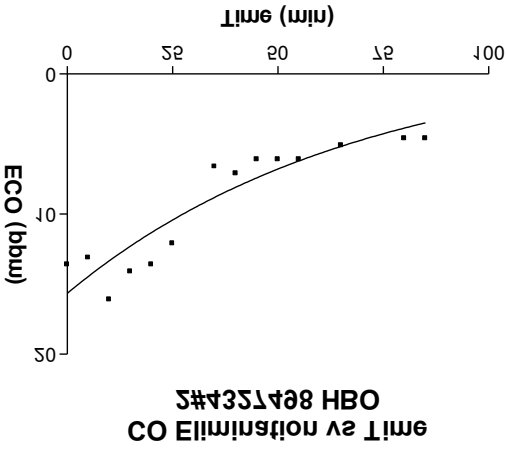

CO Elimination curve
1#0246611 HBO
CO Offgassing (mL/Min)
0.0
0.1
0.2
0.3
0.4
0.5
0
25
50
75
100
125
Time (min)

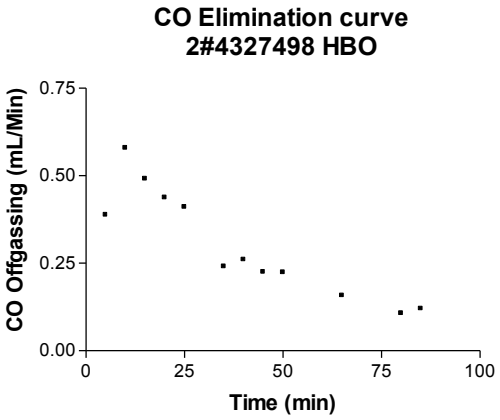

CO Elimination curve
1#4254085 HBO
ECO (ppm)
0
25
50
75
0
25
50
75
100
125
Time (min)

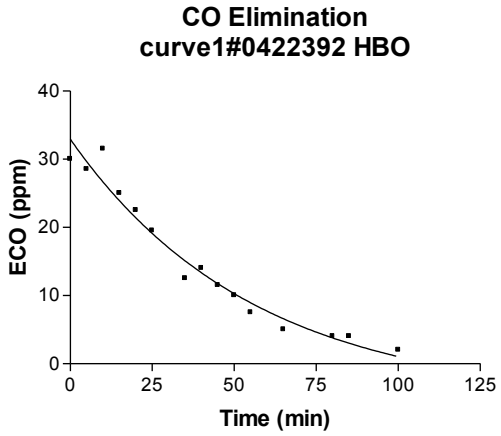

CO Elimination curve
1#4254085 HBO
CO Offgassing (mL/Min)
0.00
0.25
0.50
0.75
1.00
0
25
50
75
100
Time (min)

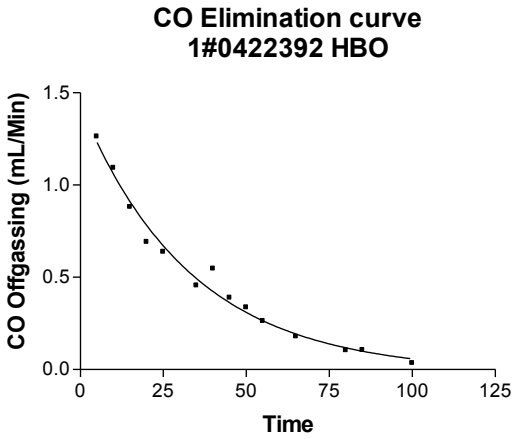

CO Elimination curve
1#4327498 HBO
ECO (ppm)
0
10
20
30
40
50
0
25
50
75
100
Time (min)

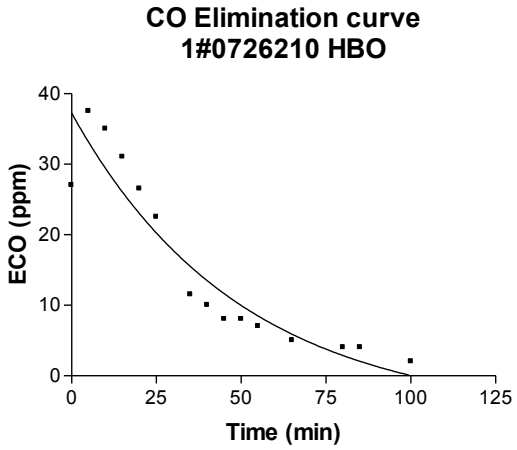

CO Elimination curve
1#4327498 HBO
CO Offgassing (mL/Min)
0.00
0.25
0.50
0.75
1.00
0
25
50
75
100
Time (min)


Time (min)
0
25
50
75
100
ECO (ppm)
0
10
20
50
CO Elimination vs Time
1#4327498 HBO


CO Elimination curve
2#4327498 HBO
CO Offgassing (mL/Min)
0.75
0.50
0.25
0.00
0
25
50
75
100
Time (min)


CO Elimination
curve1#0422392 HBO
ECO (ppm)
40
30
20
10
0
0
25
50
75
100
125
Time (min)


CO Elimination curve
1#0422392 HBO
CO Offgassing (mL/Min)
1.5
1.0
0.5
0.0
0
25
50
75
100
125
Time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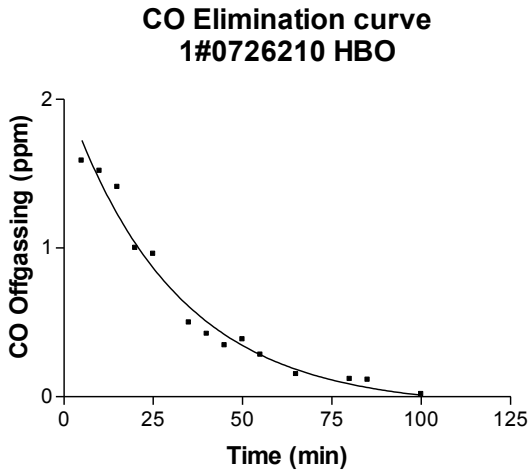
30
20
10
0
0
25
50
75
100
125
Time (min)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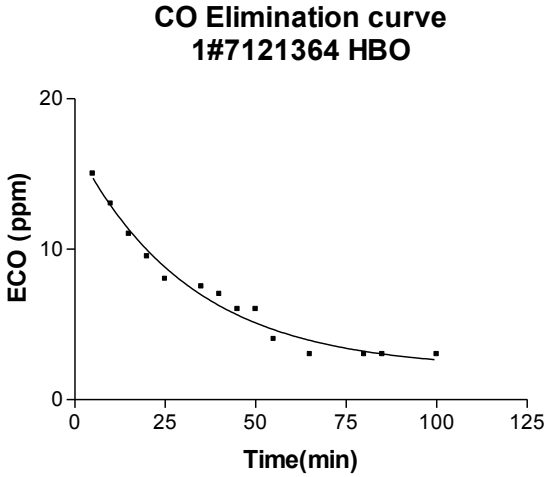
1
0
0
25
50
75
100
125
Time (min)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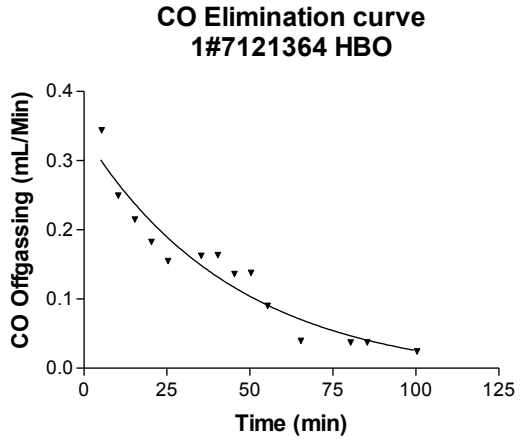
10
0
0
25
50
75
100
125
Time(min)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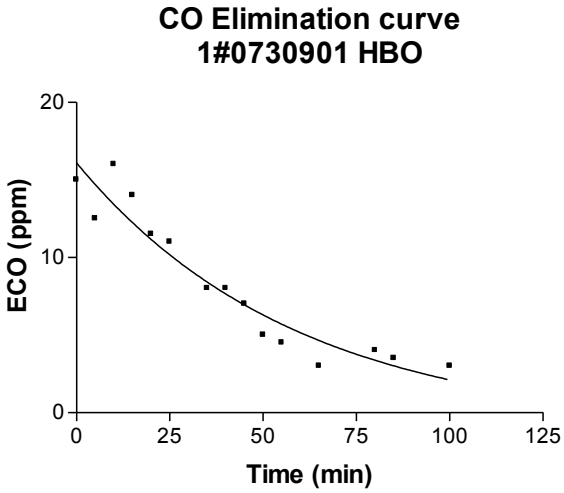
0.3
0.2
0.1
0.0
0
25
50
75
100
125
Time (min)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25
50
75
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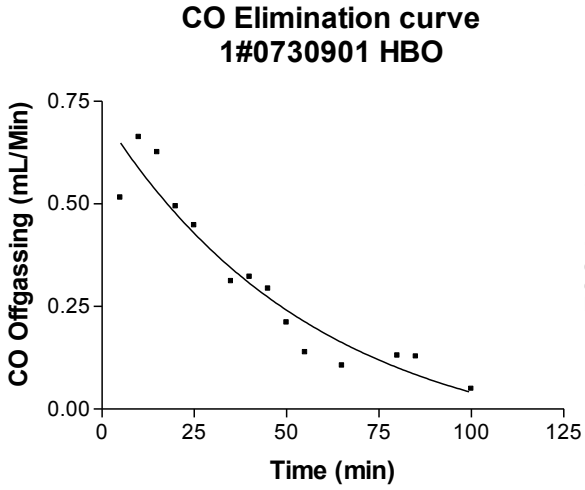
Time (min)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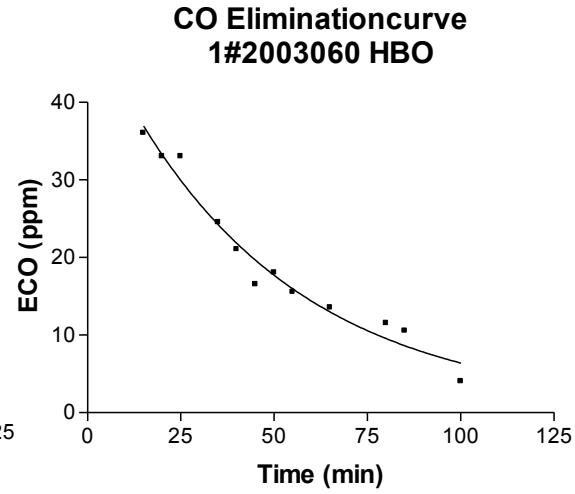
0.50
0.25
0.00
0
25
50
75
100
125
Time (min)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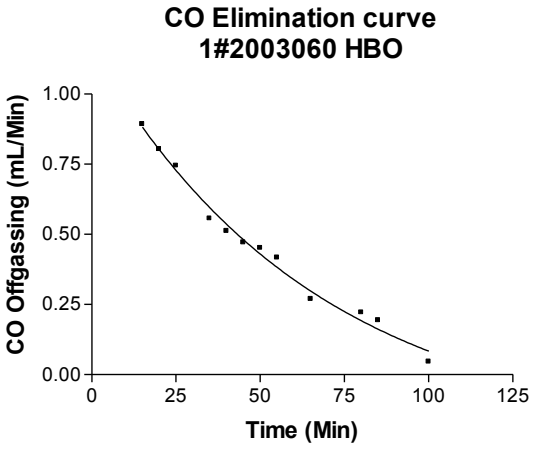
30
20
10
0
0
25
50
75
100
125
Time (min)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CO Offgassing (mL/Min)
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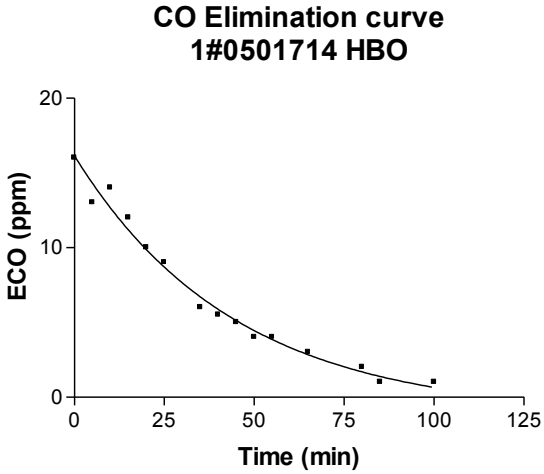
0.75
0.50
0.25
0.00
0
25
50
75
100
125
Time (Min)


CO Elimination curve
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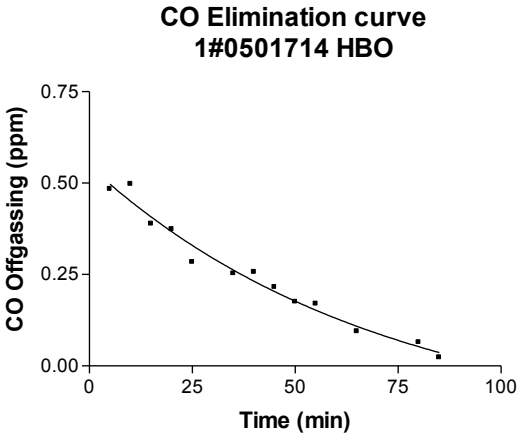
ECO (ppm)
20
10
0
0
25
50
75
100
125
Time (min)


CO Elimination curve
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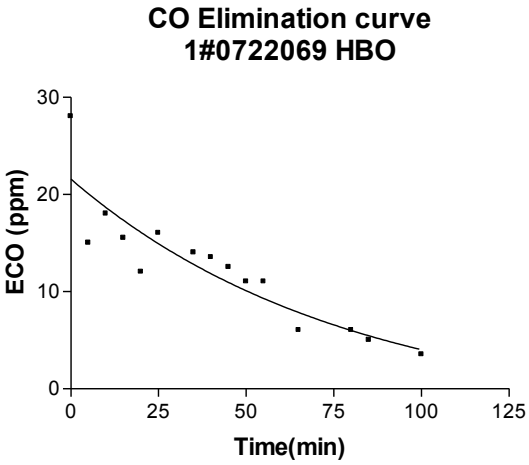
CO Offgassing (ppm)
0.75
0.50
0.25
0.00
0
25
50
75
100
Time (min)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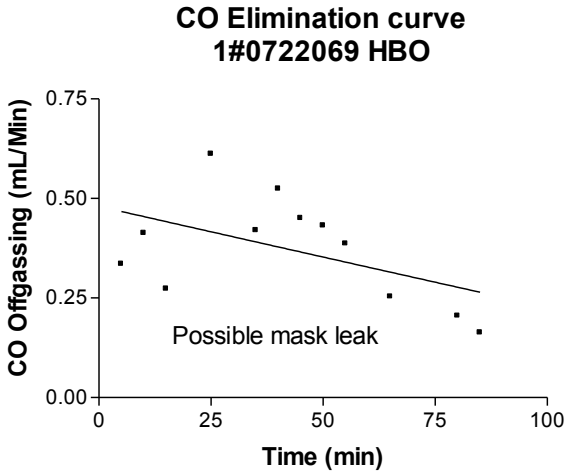
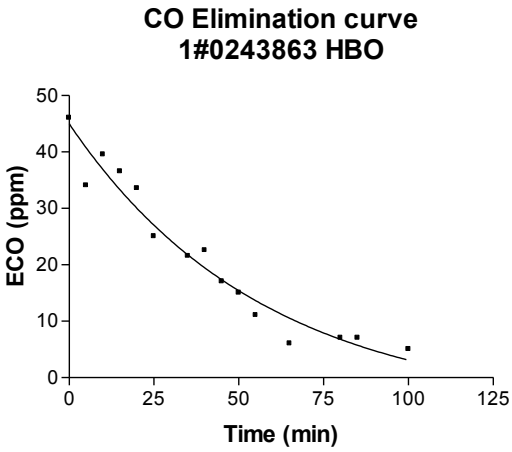
ECO (ppm)
30
20
10
0
0
25
50
75
100
125
Time(min)


CO Elimination curve
1#0722069 HBO
CO Offgassing (mL/Min)
0.75
0.50
0.25
0.00
Possible mask leak
0
25
50
75
100
Time (min)


CO Elimination curve
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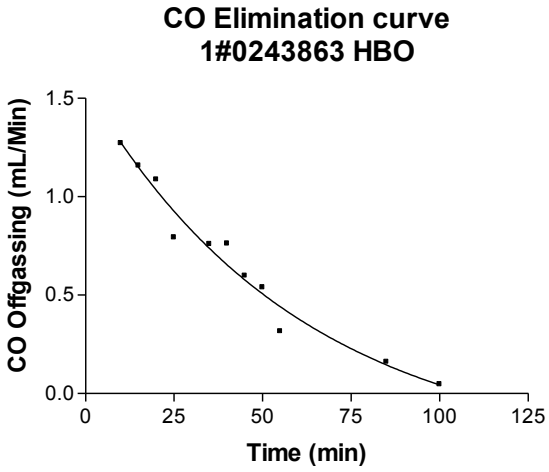
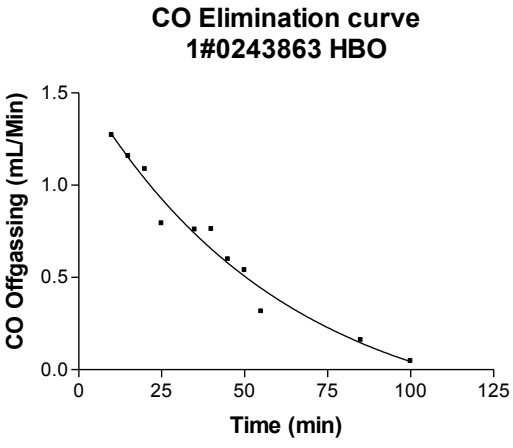
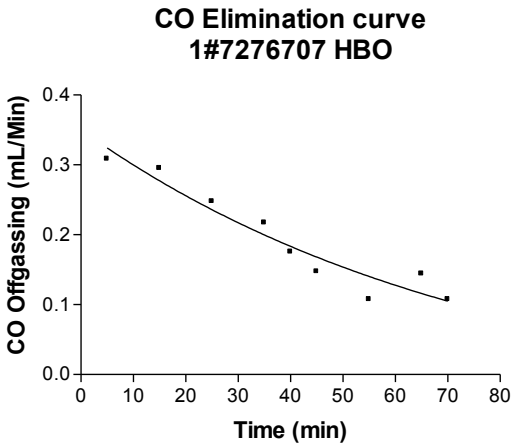
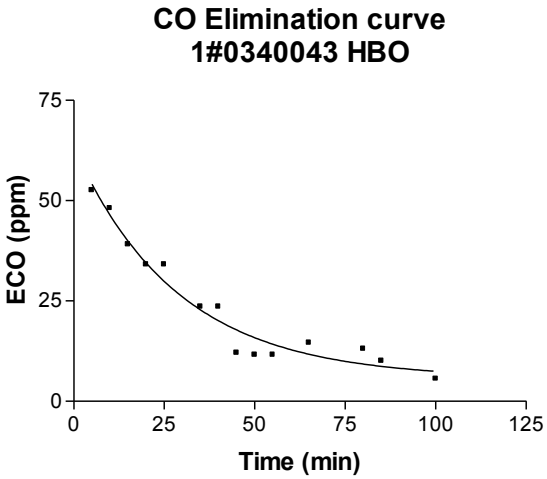
ECO (ppm)
50
40
30
20
10
0
0
25
50
75
100
125
Time (min)


CO Elimination curve
1#0243863 HBO
CO Offgassing (mL/Min)
1.5
1.0
0.5
0.0
0
25
50
75
100
125
Time (min)


CO Elimination curve
1#0243863 HBO
CO Offgassing (mL/Min)
1.5
1.0
0.5
0.0
0
25
50
75
100
125
Time (min)


CO Elimination curve
1#7276707 HBO
CO Offgassing (mL/Min)
0.0
0.1
0.2
0.3
0.4
0
10
20
30
40
50
60
70
80
Time (min)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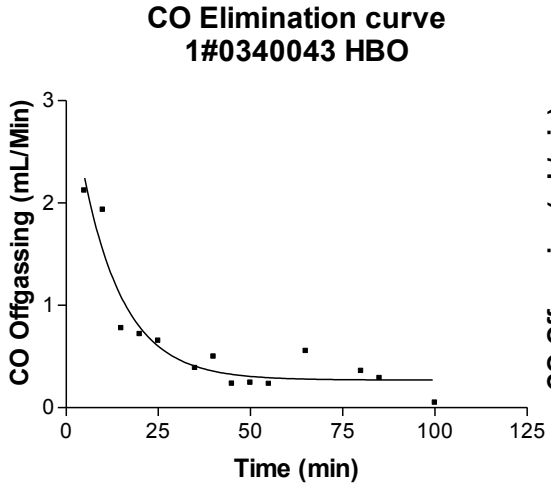
ECO (ppm)
0
25
50
75
0
25
50
75
100
125
Time (min)


CO Elimination curve
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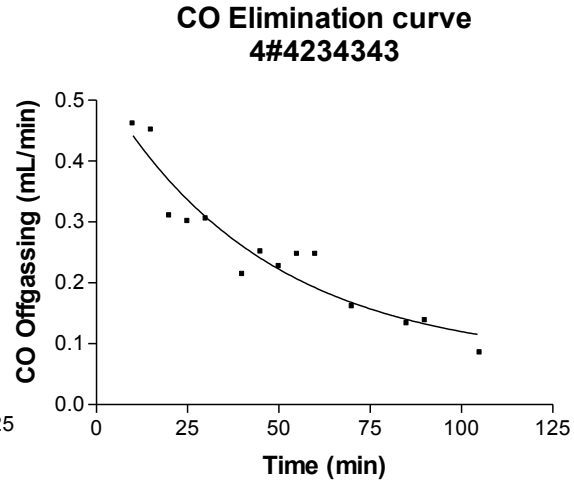
CO Offgassing (mL/Min)
0
1
2
3
0
25
50
75
100
125
Time (min)


CO Elimination curve
4#4234343
CO Offgassing (mL/min)
0.0
0.1
0.2
0.3
0.4
0.5
0
25
50
75
100
125
Time (min)

APPENDIX 18.7
DELAYED NEUROLOGICAL SEQUELAE CASE STUDY

Clinical Record

The patient, a previously healthy 75 year old male right handed non-smoker sustained a 12 hour exposure to carbon monoxide from an LPG refrigerator inside a caravan. The refrigerator was subsequently shown to have a faulty pilot burner, which was producing excessive amounts of carbon monoxide. Prior to the CO exposure he had been a very active and alert man, who had driven his car, towing a caravan, all over Australia. Earlier the same year, he had mixed concrete and built paths for his son. He had been an avid reader, taking an interest in world events, and had drawn up plans for the extension of his home, some 12 months before.

On the night of his exposure to carbon monoxide, he and his wife were on another caravan trip and were located in a caravan park at a country town near Perth, Western Australia. It had been a particularly cold night, and they spent the night with the caravan windows closed. The next morning, neighbours in other caravans became concerned that the subject and his wife were not "up and about" at their usual time of 0730 AM. By 0900 AM, the neighbours broke into the caravan and found Mr and Mrs W unconscious and unresponsive in their bed. Both were breathing and had a pulse. They carried them out of the caravan and called an ambulance. When the ambulance arrived, Mr and Mrs W were provided with oxygen by face-mask, and transported to a nearby hospital.

They were assessed at 1115 AM, and provided with 15 LPM oxygen using a Hudson mask, ECG's taken (which were normal), and IV fluids administered. Mrs W quickly regained consciousness and became alert. She was discharged at two days, after approximately 24 hours of oxygen therapy. Mr W's conscious state improved to GCS 13 after 4 hours of oxygen. However, he remained confused, lethargic and somnolent for 48 hours, and received virtually continuous 15 LPM oxygen by facemask during this period. After 4 days in hospital, he had returned to normal, according to his relatives, and he was discharged from hospital. The diagnosis at discharge was toxic gas inhalation, and it appeared that the possibility of carbon monoxide poisoning had not been considered. Over the next month, Mr W underwent a significant deterioration in his overall level of functioning:

He had significant deterioration in his gait, requiring assistance to walk even around his house. The difficulties were most noticed with the initiation of walking, and he had been falling.

He confused sliding doors for hinged doors

He had significant problems with dressing, for example he would put two socks on his right foot. He was unable to put his trousers, shirt or pullover on without assistance.

He was disorientated with determining left versus right.

He could no longer read or write.

His personality became “flat” and he did not initiate spontaneous conversation.

He became emotionally labile, and lacked insight into his condition, although he demonstrated some evidence of frustration at his loss of short-term memory

He developed significant difficulties with his short-term memory, being unable to remember even conversations from a few hours before, or the events of the previous day.

He became incontinent of urine and faeces

Given the level of disability outlined above, he was not capable of driving his car.

Mr W had consulted three different doctors (including a specialist neurologist) in the intervening four weeks. He also had received a CT scan of his brain and this was reported as normal. His GP identified the causal link between his exposure to carbon monoxide, and the subsequent deterioration in his neurological and cognitive function. After identifying Mr W’s clinical condition as a delayed relapse from carbon monoxide exposure, he was referred to the Hyperbaric Medicine Unit at Fremantle Hospital for assessment.

When examined, he had normal vital signs; pulse rate 90, BP 110/70. Respiratory, gastrointestinal and cardiovascular examinations were unremarkable. His Glasgow coma score was 14, being unable to provide details of where he was when examined. He scored 15/30 when tested with a mini-mental state examination. His main deficits were in orientation (unable to provide day, date, year, where he was), serial sevens, and short-term recall. He was unable to undertake the symbol -

digit test, due to lack of comprehension about its meaning, and his immediate recall was 6 digits forwards, and 3 digits backwards. He was also unable to write a sentence or even his name, and could not copy a diagram. He could read sentences, but could not recall what he had read, or the meaning of the sentence when questioned only minutes later. Mr W was unable to perform simple mathematical tasks, for example adding, multiplying single digit numbers.

Cranial nerve examination demonstrated visual inattention in the left visual field, and positive glabellar and positive palmomental signs. Cranial nerves were otherwise normal. Mr W had a pill-rolling tremor of the right hand. He could not stand for the Romberg test without assistance, because he fell backwards. He required a broad-based stance and his difficulty with standing was no worse with the eyes closed. There were problems with initiation of gait, similar to that observed with Parkinson's syndrome. Mr W's gait was broad based and apraxic and he could not walk without assistance because of the falling backwards.

He had generally increased tone, with equal and normal power in all four limbs. Tests of coordination showed no cerebellar signs, with loss of the tremor with action, and slow (but normal) finger-nose tests. There was right versus left disorientation when asked to perform a three-stage task such as "with your left little finger, please touch your nose then your right ear". Hyperreflexia was demonstrated in the right arm compared with the left, but lower limb reflexes were otherwise within normal limits, and plantar reflexes were downgoing. Sensation was preserved in all four limbs, however sensory inattention was noted for the left side.

The clinical neurological findings pointed to a deficit in the non-dominant (right) hemisphere cortical region, with early evidence of a Parkinson-like syndrome affecting gait, and the right arm (basal ganglia). The left-right disorientation, dyscalculia and problems with writing were consistent with a Gerstmann-like syndrome involving the dominant hemisphere. In addition there were deficits in short-term memory and ongoing registration of events, coupled with urinary and faecal incontinence. When examined at the Hyperbaric Medicine Unit, the only blood test performed was a COHb level that was zero. Carbon monoxide offgassing measurements were 1 ppm breathing air, and 3 ppm breathing NBO.

Mr W was treated with a course of HBO, commencing with twice-daily 2.8 ATA treatments (18:60:30 tables) followed by eight daily 2.0 ATA treatments (10:100:10 tables). Over the course of the two weeks he progressively improved, to be able to score 29/30 on the MMSE, recite 7 digits forward and 4 backward with the digit recall test, score 31 on the symbol-digit test, draw a clock face, read and remember single sentences. In addition, his incontinence recovered, he was able to walk normally, and dress himself. He had returned to a level of full self-care according to his wife. There were still difficulties noted with some complex mechanical tasks, and Mr W reported that he could no longer undertake complex drawing tasks such as drawing plans for a house as he "could not put the pieces together".

He was sent for formal neuropsychological testing, which demonstrated a general compromise to his level of intellectual functioning, particularly involving the non-dominant hemisphere. Testing demonstrated scores in the average to high average ranges on the Wechsler Adult Intelligence Scale (Revised). He had difficulties with visuo-spatial construction. Errors were made when copying a complex graphic figure. His immediate memory was within normal limits, and short term memory for verbal logical material was normal. He had significant deficits in short term memory for designs. There was a poor rate of learning for new material. Manual motor speed was slow bilaterally, and there was finger agnosia and sensory inattention on the left side.

Mr W was discharged after the two-week course of HBO treatment, for follow-up at one month, three months and eight months.

At one month, he remained at the same level of functioning, and there had been no regression. His MMSE was 30/30 and symbol-digit and digit-recall scores were improved to 7 digits forward and 5 digits backward. By three months after HBO treatment, he was again driving his car.

At eight months, he received another formal neuropsychological test. This showed that he had improved markedly in his short-term memory for visual designs, while maintaining his verbal short-term memory. His rate of new verbal learning had also improved. His sensory agnosia and inattention of the left hand had disappeared. His main remaining deficit was for visuo-spatial constructional tasks. Overall, his level of functioning in the domestic environment had returned to

normal, although he reported that he now had to carefully plan all of his activities, because of being slower and less adaptable when undertaking complex tasks.

His wife was also assessed, as she clearly had been exposed to a similar environment, and had noted some intermittent problems with memory and balance early after discharge, however by 4 weeks, she had fully recovered. She had no symptoms, normal neurological and cognitive function, and her family reported that she had normal level of functioning in her domestic and social environments. She was offered treatment with HBO at the same time as her husband, but declined this offer.

APPENDIX 18.8 RESEARCH SUBMISSION, CONSENT FORMS AND ETHICS APPROVAL

THE EFFECT OF HYPERBARIC OXYGEN

ON

CARBON MONOXIDE

OFF-GASSING

INVESTIGATORS AND QUALIFICATIONS:

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Applicant:	Dr Paul Mark
Qualifications:	MBBS DIP RACOG FACEM DIP DHM
Department/Position:	Department of Emergency Medicine Staff Specialist
Address:	Fremantle Hospital Alma Street FREMANTLE WA 6160

Applicant:	Dr Neil Banham
Qualifications:	MBBS FACEM
Department/Position:	Department of Emergency Medicine Staff Specialist
Address:	Fremantle Hospital Alma Street Fremantle WA 6160

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BACKGROUND INFORMATION

Carbon monoxide (CO) is a colourless and odourless gas produced by incomplete combustion, and which may be lethal when inhaled by humans. Individuals may be exposed to the gas in both domestic and industrial situations. The exposure may be accidental or as a result of a suicide attempt. It is the commonest agent used in suicide by poisoning in Australia.[1] Ten to 40% of survivors of a non fatal poisoning can suffer neurological or psychiatric sequelae.[2] Treatment of CO poisoning is with oxygen and improved outcome has been demonstrated with the use of oxygen under pressure, hyperbaric oxygen (HBO). In particular, a significant reduction in delayed neurological and psychiatric sequelae has been noted with the use of HBO for CO poisoning.[3]

Carbon monoxide exerts its toxic effect on the body in a number of ways. It binds to haemoglobin 240 times more avidly than oxygen[4], and creates a functional anaemia. The CO also moves the oxyhaemoglobin dissociation curve to the left, further reducing oxygen delivery to the tissues.

Carbon monoxide binds to myoglobin and 15% is found in extravascular tissues.[5] Its interference with cerebral autoregulation exacerbates brain ischaemia due to impaired myocardial contractility.[6] Carbon monoxide exerts a toxic effect at a cellular level by binding to the cytochrome enzymes; cytochrome P450, A, A3 and cytochrome C oxidase.[7] This binding occurs with less affinity than that which oxygen binds to cytochromes, but it is thought to be accelerated by hypoxia. In 1975, Goldbaum and colleagues[8], demonstrated that dogs exposed to carbon monoxide sufficient to produce COHb levels of 54-90%, died. Dogs rendered anaemic and subsequently transfused with red cells containing 80% COHb to produce final carboxyhaemoglobin levels of 57-64%, survived. This indicated that it is not the COHb which causes death. It is most likely due to poisoning at a cellular level. This cellular toxicity may be the cause of delayed neurological and psychiatric sequelae in humans.

Traditionally, the COHb level has been used as an indicator of severity of poisoning. This has been shown to be of low predictive value and patient outcome does not correlate well with COHb levels measured in hospital.[3,9,10] Also, titration of treatment against the COHb concentration is often unsuccessful.[3,11] It is known that there is a group of patients who suffer delayed neuropsychiatric sequelae despite the return of their COHb levels to normal.[2,3,12] The COHb level is not a useful predictor of these delayed sequelae.

Patients with acute CO poisoning and delayed neurological or psychiatric sequelae have been successfully treated with hyperbaric oxygen.

The purpose of HBO therapy is two fold. Firstly it accelerates the removal of CO from Haemoglobin (Hb), myoglobin and cytochromes. The half-life of COHb in air is 320-480 minutes. This is reduced to 60-80 minutes by 100% normobaric oxygen and to 8-23 minutes by HBO at 2.8 atmospheres absolute.[7,9,13,14] At this pressure the arterial partial pressure of oxygen is around 1800 mmHg which should displace any remaining CO from the cytochromes. Intense vasoconstriction rapidly reduces cerebral oedema whilst increasing cerebral oxygen flux. Numerous published case reports attest to the ability of HBO to awaken a patient whose COHb level has been zero for hours, and to the additional benefits of subsequent treatments in patients with persistent deficits.[15,16,17]

Secondly, it prevents delayed neuropsychiatric sequelae. In a study by Myers, two groups of patients were studied.[3] Those with a normal psychometric score, normal ECG and a COHb level less than 30% received normobaric 100% oxygen. Delayed sequelae developed in 12%. The more severely affected patients with gross neurological signs, psychometric abnormalities or a COHb level greater than 30% received HBO at 2.8 atmospheres. There were no delayed sequelae. Those patients who developed delayed sequelae following normobaric oxygen were later treated with HBO and all recovered.

Gorman and Runciman[13] in a major review of CO poisoning literature in 1991, stated "a reliable marker of the severity of CO poisoning is urgently needed so that trials of alternative regimens of treatment can proceed." In the absence of this marker, at the Fremantle Hospital Hyperbaric Medicine Unit, clinical assessment takes into account;

1. A history of exposure to carbon monoxide.
2. Presence of an altered conscious state at any stage or impaired higher mental function when examined.
3. Presence of an elevated COHb level (normal is less than or equal to 1%, smokers may have less than or equal to 8%).

Greater emphasis tends to be placed on detection of impaired mentation because this is the only useful test of significant intoxication with carbon monoxide that is currently available. This criterion may become less specific if other toxins (for example ethanol or sedatives) have been ingested concurrently with the poisoning of carbon monoxide.

In 1985, Willms and co-workers[18] demonstrated increased "off-gassing" (exhalation of carbon monoxide) in carbon monoxide poisoned patients when treatment was with hyperbaric oxygen, compared with 100% oxygen at one atmosphere. Expired CO was increased during hyperbaric oxygen despite normal COHb levels. No follow-up to this study has been published in the literature.

This effect of CO "off-gassing" when patients are treated with hyperbaric oxygen has great potential for use as a marker of persisting total body load of carbon monoxide. It constitutes a measurable end-point against which all treatment regimens can be titrated. It is with this background that the following research is proposed at the Fremantle Hospital Hyperbaric Medicine Unit.

PROBLEM TO BE STUDIED

To examine the phenomenon of Carbon Monoxide offgassing, in control subjects, smokers and non-smokers, and to examine the effect of hyperbaric oxygen on carbon monoxide off-gassing in carbon monoxide poisoned patients, and correlate this with their neurological and psychometric status.

PURPOSE OF THE RESEARCH AND ITS SIGNIFICANCE

The purpose of the research is to examine carbon monoxide off-gassing and its relationship with hyperbaric oxygen therapy, in an effort to use this modality as a marker of persisting toxicity. The technique used in the proposed study has potential clinical applications in a number of areas:

1. As a marker of poisoning in circumstances when much time has elapsed since rescue and measured COHb is normal despite a history of exposure; or where other mind altering substances have also been ingested.
2. As a guide to the need for further hyperbaric oxygen therapy. If patients are continuing to excrete CO in their breath, this indicates body stores of carbon monoxide are still high.
3. If the persistent off-gassing of carbon monoxide correlates with persistent impaired psychometric testing, then it has a potential as a hard sign of persistent CO intoxication. It can also be performed in ventilated patients.
4. The test for CO in expired air has potential for use as a quick inexpensive test for carbon monoxide poisoning in Emergency Department patients. This would obviate the requirement to perform a COHb level on patients with carbon monoxide poisoning and hence would save money in laboratory analysis costs.
5. Carbon monoxide off-gassing may be used for further studies relating to ideal oxygen dose when treating CO poisoned patients. If the use of HBO continues to improve the clinical condition of patients beyond the point when body stores of CO return to normal, then some other mechanism may explain the efficacy of HBO.

Fear of persisting CO load has persuaded many hyperbaric physicians to continue treatment at 2.8 atmospheres. If CO excretion could be demonstrated to have ceased, there is theoretical evidence to suggest that treatment at 2.0 atmospheres produces better cerebral salvage. Hyperbaric treatment at 2.0 atmospheres is convenient and economical. It is the pressure at which elective patients are treated daily in the Hyperbaric Medicine Unit and obviates the need for a second chamber to be activated. There are significant economies in terms of nurse attendant nitrogen loads if 2.0 atmosphere tables could be used for follow-up treatment of the CO poisoned patient after the initial 2.8 atmosphere treatments.

OBJECTIVES OF THE RESEARCH

1. To determine if excretion of carbon monoxide is enhanced by hyperbaric oxygen and to compare this with excretion under normobaric conditions using air and 100% oxygen.
2. To correlate excretion of CO with the patient's psychometric status, which is currently the only method of assessing ongoing intoxication with carbon monoxide.
3. To correlate excretion of CO with the duration and severity of exposure to CO, as gained from the patient's history.
4. To attempt to calculate a tissue half-life of carbon monoxide which will be possible if there is continued excretion of carbon monoxide from the patient's body after their COHb levels have returned to normal.
5. To determine the amount of CO Offgassing which occurs in controls, including Divers receiving treatment for decompression illness.

RESEARCH DESIGN

The normal treatment regimen for carbon monoxide poisoned patients will be followed. This currently consists of a minimum of two treatments on a FH18 metre table (see Data Collection Form 2), followed by further FH18 tables if the patient demonstrates ongoing toxicity or an FH10 table if the patient has returned to a neurologically normal state at the end of the second treatment.

The normal treatment regimen is as follows:

Patients are clinically assessed at presentation by full history and examination. An intravenous cannula is inserted and blood taken for COHb level and lactate level. A mini mental state examination is then performed and a decision made to start treatment on the basis of the history of exposure, a history of altered mental state after exposure, abnormalities detected in mental state or neurological examination or significant COHb levels detected. Treatment proceeds as per the flow chart number 1.

Further clinical assessment of the patient occurs between treatments and the decision to continue treatment is based on abnormalities detected at these examinations. Normally, no further blood samples are taken, apart from lactate levels.

In this study, most of the data collection will be purely observational and will not require any invasive intervention. All standard regimes of treatment and assessment will be followed. The only deviations from normal practice are outlined in flow chart number 2. It is planned to take additional blood samples for COHb and lactate levels at the end of the first hyperbaric oxygen treatment and at the commencement of subsequent hyperbaric oxygen treatment. This should result in minimal discomfort to the patient, because the blood sample can be taken from the intravenous cannula which is already in situ. This will require a small amount of extra blood to be withdrawn prior to the sample, in order to avoid stagnation and dilution by bung flushes. All other measurements will be of carbon monoxide concentration in the patient's exhaled gas, using a Dräger® Ecolyser carbon monoxide analyser. The exhaled gas is normally dumped outside the hyperbaric chamber. The proposed study is outlined in the data collection form, with breath samples every five minutes during treatment. Measurements of respiratory minute volume would be performed when the measurements of CO concentration are made, using a spirometer in series with the overboard dump.

PATIENT SELECTION

1. The population to be studied

All patients presenting to the Fremantle Hospital Hyperbaric Medicine Unit requiring hyperbaric oxygen for acute carbon monoxide poisoning will be studied. An information sheet will be given to each patient (see

Appendix 3) and written consent will be sought before they are entered into the study. Any patients unable to give their consent and who do not have available next of kin or relatives to give consent if the patient has altered conscious state, will be excluded from the study.

2. Sample size

As the number of patients with carbon monoxide poisoning who present on an emergency basis in any given period cannot be controlled, no formal evaluation of numbers for statistically significant results has been made. It is hoped to obtain a sample size of approximately 30 patients.

Analysis of the patient's exhaled gas will measure carbon monoxide content of each sample directly. As normal content is practically zero (smokers have levels above zero), this will be irrefutable data. The calculation of the total CO off-gassing is indirect and subject to some error, but from a zero baseline will provide significant quantitative data.

3. Criteria to be used for selecting participants

As mentioned in `1', all patients with carbon monoxide poisoning who present for treatment in the Hyperbaric Medicine Unit who have not been excluded, will be entered into this study, after consent is obtained.

4. Control Population

It is proposed to use a population of divers who require recompression therapy in the hyperbaric chamber as controls for similar exhaled gas measurements. Written consent will be obtained from each diver prior to their participation. On past experience, the number of divers presenting yearly is approximately equal to the number of CO poisoned patients. Both population are treated with 18 metre (2.8 atmosphere) tables. Divers routinely have blood samples taken for electrolytes and full blood picture when they present, and a COHb level can be determined from these samples. This will establish a baseline COHb level this group, just prior to their recompression in the chamber. If the initial five exhaled gas samples from the divers are negative for carbon monoxide, no further intervention will occur. Volunteer smokers and non-smokers will be approached to obtain baseline control values for CO offgassing. Permission will be sought from these individuals for a blood sample to correlate CO offgassing with COHb.

ETHICAL CONSIDERATIONS

These relate mostly to the collection of additional blood samples for COHb.

1. From the CO poisoned patients a) at the end of the first HBO treatment and b) at the start of subsequent HBO treatments.
2. From divers treated in the chamber.

Written consent will be obtained from the patients before these blood samples were taken. As all carbon monoxide poisoned patients and many divers already have intravenous cannulae in situ, the blood samples will be taken from this cannula to minimise discomfort to the patients.

The remaining sampling of expired gas from the chamber is purely observational and does not alter current protocols of management. All patients would receive the same treatment as is currently given in the chamber. Sampling from the overboard dump outside the chamber does not interfere with the patients treatment or safety in any way.

3. From control subjects - smokers and non-smokers. This will strictly be on a voluntary basis. It is planned to link the control arm of the trial to a quit smoking campaign, so that blood samples taken at the time of the campaign could be used to correlate with CO offgassing.

APPROVAL BY OTHER ETHICS COMMITTEES

This project has been considered by the Human Ethics Committee of Royal Adelaide Hospital and has been approved for research to proceed at that Hospital along similar lines. It is proposed that the data obtained from the Fremantle Hospital will be able to be combined to form a multi centre trial which should be publishable in a Journal of Hyperbaric Medicine or Toxicology.

TIME FRAME FOR THE STUDY

It is proposed to run this study during the 12 calendar months after it is approved and when all equipment is functional for the commencement of the study. This is likely to be from June 1992 to June 1993.

THE IMPACT THE STUDY WILL HAVE ON OTHER STAFF

Apart from collection of additional blood samples, all data collection and gas sampling will be performed by the investigators. The study will not require additional resources for the Hyperbaric Medicine Unit. Additional COHb assays will be required. The anticipated number will be twice the number of patients in the study ie. approximately 80 assays.
The impact on nursing staff in the Unit will be limited to:

1. Ensuring adequate patient co-operation for obtaining exhaled gas samples during air breaks.
2. Switching divers from a Scott mask to a Duke's Hood for oxygen delivery.
3. Communicating respiration rate and vital signs at normal intervals with the investigators.

SUMMARY

Carbon monoxide (CO) is the commonest agent used for suicide by poisoning in Australia. It exerts its toxic effect by combining with haemoglobin (the oxygen carrying protein of the blood) and also by poisoning cellular metabolism of the body. Patients affected by CO become generally unwell, have reduced heart and muscle function, and neurological impairment, ranging from subtle defects in higher mental function to loss of consciousness and fitting.

Treatment of CO poisoning is with oxygen as well as full life support if necessary. Improved outcome has been demonstrated by treating patients with oxygen under pressure, hyperbaric oxygen (HBO). Because much of the poisoning is at a cellular level, the poisoning is difficult to measure objectively. The carbon monoxide bound to haemoglobin (COHb) is unreliable as a marker of the patients' clinical condition. Detailed neurological and psychometric testing is currently the best available method of monitoring response to treatment.

A recent study has shown that patients continue to excrete carbon monoxide from their body after the COHb returns to normal and that this excretion (or off-gassing) is enhanced by hyperbaric oxygen. This off-gassing of carbon monoxide is likely to be a more reliable marker of CO poisoning than all currently available methods.

In this study, it is planned to measure off-gassing of carbon monoxide by patients who have CO poisoning, while they receive standard therapy with hyperbaric oxygen. Exhaled gas samples will be measured in the outside exhaust gas of the chambers while the patient is treated. A population of divers being treated for recompression illness will be used as controls.

The additional interventions for each patient will be minimal, limited to two or three extra blood samples. All measurements of exhaled gas will be performed on the exhaust gases of the chamber and will not affect the patient in any way. Standard treatment regimens will be used for all patients. The study period will be over approximately 12 months and involve 30-40 patients with CO poisoning.

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THE EFFECT OF HYPERBARIC OXYGEN ON CARBON MONOXIDE OFF-GASSING INFORMATION SHEET FOR PATIENTS

Doctors at Fremantle Hospital are currently conducting a detailed study of the effect of hyperbaric oxygen on patients with carbon monoxide poisoning.
The purpose of this study is to measure the amount of carbon monoxide which is excreted in the breath during the standard treatment in the hyperbaric chamber. It is hoped to gain information which will help us plan ideal treatment schedules for each individual patient.
You will receive the normal treatment during this study. The only change from usual protocol will be to take two or three extra blood samples during the course of your treatment. This enables doctors to correlate the breath sample measurements with blood levels of carbon monoxide.
As you breathe oxygen in the chamber, your exhaled breath is usually "dumped" outside the chamber. This will be measured for carbon monoxide content by doctors as it passes out of the exhaust system of the chamber. You will not notice any difference to your breathing because all of the gas is measured when it is outside the chamber.
If you do not wish to be a participant in the study we will proceed with the standard treatment, which does also involve some blood samples being taken, but not as many as if the study were conducted.
You are free to withdraw your consent at any time without prejudice to your relationship with your doctor of this Hospital. All information collected is confidential and any published results will be in a statistical form and not identify individuals by name. Thank you for your participation.

I _____ consent to _____ participating in the trial "The effect of hyperbaric oxygen on carbon monoxide off-gassing".

Signed:_____ Date: _____

Witness: _____ Date: _____

Contact number for enquiries:

Dr David Smart/Dr Harry Oxer
Hyperbaric Medicine Unit
Fremantle Hospital
FREMANTLE WA 6160

Phone: (09) 431 2233

THE EFFECT OF HYPERBARIC OXYGEN
ON CARBON MONOXIDE OFF-GASSING
INFORMATION SHEET FOR DIVERS

Doctors at Fremantle Hospital are currently conducting a detailed study of the effect of hyperbaric oxygen on patients with carbon monoxide poisoning.

As part of any scientific study, a "control" group of patients is needed. This enables doctors to compare the group of patients they are treating with another group of patients who are not affected with the same condition. We would like to use divers who are being treated for decompression illness as controls for this study.

The purpose of this study is to measure the amount of carbon monoxide excreted in patients breath during a standard treatment in the hyperbaric chamber. It is hoped to gain valuable information which will help us plan ideal treatment schedules for each patient with carbon monoxide poisoning.

It is expected that measurements taken on divers will show virtually zero levels of carbon monoxide. The measurements need to be taken to ensure that any deviation from zero measured in carbon monoxide poisoned patients is due to their exposure to carbon monoxide and not just related to treatment.

You will receive the normal treatment for your decompression illness. The only change from the usual protocol will be to taken an extra blood sample before your treatment with hyperbaric oxygen. All other measurements will be performed on your exhaled gas which is normally "dumped" outside the recompression chamber to the atmosphere.

As you breathe oxygen in the chamber you will not notice any changes when the exhaled breath samples are measured for carbon monoxide content because they are collected outside the chamber from its exhaust system. Samples will only be taken for five readings if they are negative for carbon monoxide.

If you do not wish to be a participant in the study, we will proceed with your standard treatment for decompression illness. You are free to withdraw your consent at any time without prejudice to your relationship with your doctor of this Hospital. All information collected is confidential and any published results will be in a statistical form and will not identify individuals by name. Thank you for your participation.

I _____ consent to participate in the trial "The effect of hyperbaric oxygen on carbon monoxide off-gassing".

Signed: _____ Date: _____

Witness: _____ Date: _____

Contact number for enquiries:

Dr David Smart/Dr Harry Oxer
Hyperbaric Medicine Unit
Fremantle Hospital
FREMANTLE WA 6160

Phone: (09) 431 2233

CARBON MONOXIDE OFF-GASSING AS A MARKER OF CARBON MONOXIDE POISONING
INFORMATION SHEET FOR VOLUNTEER PARTICIPANTS

Doctors at Fremantle Hospital are currently conducting a detailed study measuring breath samples from patients with carbon monoxide poisoning.
As part of any scientific study, a "control" group of subjects is needed. This enables doctors to compare the group of patients they are treating with another group who are not affected with the same condition. We would like to use volunteers as controls for this study.

The purpose of this study is to measure the amount of carbon monoxide excreted your breath, breathing air and 100% oxygen. It is hoped to gain valuable information which will help us plan ideal treatment schedules for each patient with carbon monoxide poisoning.

It is expected that measurements taken on volunteers will show low levels of carbon monoxide. Smokers are known to excrete higher levels of CO, and samples collected from them will be equally useful for the study. The measurements need to be taken to ensure that any deviation from zero measured in carbon monoxide poisoned patients is due to their exposure to carbon monoxide and not due to other causes. We would like to correlate the breath samples with a blood sample from volunteers who agree to provide blood. If you do not wish to provide a blood sample, then we would still like to measure your breath samples.

As you breathe air or oxygen, you will not notice any discomfort when the exhaled breath samples are measured for carbon monoxide content because they are collected from your exhaled breath. Samples will only be taken for five readings if they are negative for carbon monoxide.

If you do not wish to be a participant in the study, we will not proceed further. You are free to withdraw your consent at any time without prejudice.
All information collected is confidential and any published results will be in a statistical form and will not identify individuals by name. Thank you for your participation.

I _____ consent to participate in the trial "Carbon Monoxide offgassing as a marker of Carbon Monoxide Poisoning".

Signed: _____ Date: _____

Witness: _____ Date: _____

Contact number for enquiries:
Dr David Smart/Dr Harry Oxer
Hyperbaric Medicine Unit
Fremantle Hospital
FREMANTLE WA 6160

Phone: (09) 431 2233

Data Collection Forms

DATA COLLECTION FORM 1

THE EFFECT OF HYPERBARIC OXYGEN ON
CARBON MONOXIDE OFF-GASSING
DATA COLLECTION FORM

Unit Medical Record Number: _____
Record of Exposure to CO: _____
Time of Exposure: _____
Type of Exposure: _____
Time of rescue: _____
Condition at time of rescue: _____
Treatment received:
(O_2 concentrations/times)

.....
.....
.....
.....
.....
.....
.....
.....
.....
Is patient a smoker? Yes/No _____
Were any other drugs/alcohol used? _____
Was this exposure due to parasuicide _____
Mental State Examination Score (in ED) _____
Initial COHb level _____
Time taken _____
Initial lactate level _____

Other COHb levels: Lactate levels

1. Pre-first HBO tmt _____

2. Post-first HBO tmt _____

3. Pre-second HBO tmt _____

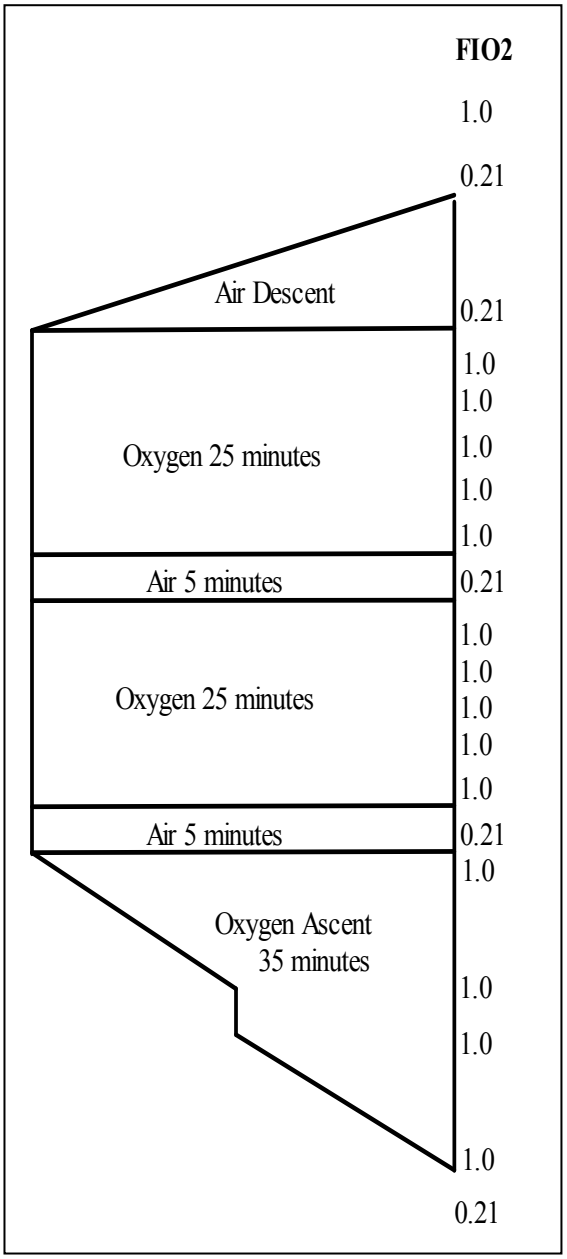
4. Pre-third HBO tmt _____

DATA COLLECTION FORM 2

Treatment Number

Patient Sticker

FH 18 Table
Exhaled Gas Samples



Sample	ECO Concentration (ppm) 1	2	Avg	RMV (litres)	Volume CO offgassed RMV x [CO] x Time	Oxygen Analyser %
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
Total CO Offgassed						

DATA COLLECTION FORM 3

100 Percent Oxygen treatment

NBO Data Collection Sheet Data at 10 minute intervals Sample	ECO (ppm) Concentration			RMV (Litres)	CO Volume Offgassed	Oxygen Analyser %
	1	2	Avg			
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
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39						
40						

DATA COLLECTION FORM 4

CARBON MONOXIDE POISONING

DATE_____ PATIENT NAME_____

Please obtain the following information and forward with the patient to the Hyperbaric Medicine Unit:

1. Time of onset of exposure to CO:
2. Source of exposure to CO:
3. Time of rescue:
4. Duration of exposure to CO:
5. Time of loss of consciousness and duration
6. OXYGEN TREATMENT DELIVERED OVER TIME

Time
FIO2 or Flow Rate
Oxygen Delivery System Used

7. Initial MMSE Score:
8. Initial COHb level and time taken:
9. Ethanol level (if available):
10. Tricyclics detected (yes/no):
11. Arterial Blood gas Result:
12. Full Blood Picture:
13. Electrolyte results:

DATA COLLECTION FORM 5

Additional Data	Patient Label			
Is patient a smoker?				
Was this a suicide attempt?				
Source of Carbon Monoxide?				
	MMSE	COHb	Lactate	Time
Initial Level ED				
Pre first HBO Treatment				
Post first HBO Treatment				
Pre 2nd HBO Treatment				
Post 2nd HBO Treatment				

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MKW:VH

13 March 1992

Dr D. Smart
Dr H. Oxer
Dr P. Mark
Fremantle Hospital

Dear Doctors

Re: Protocol for Research Project: The Effect of Hyperbaric Oxygen on Carbon Monoxide Off-Gassing

The above protocol was considered at the 10 March 1992 Meeting of the Research Committee. The Committee approved the scientific validity of the study and has forwarded the protocol to the Human Rights Committee for consideration.

Yours sincerely

Michael K. Walsh
DIRECTOR, CLINICAL SERVICES
SECRETARY, RESEARCH COMMITTEE

A58A

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GMG:VH

26 May 1992

Dr H.F. Oxer
Director
Hyperbaric Medicine Unit
Fremantle Hospital

Dear Dr Oxer

Re: The Effect of Hyperbaric Oxygen on Carbon Monoxide Off-Gassing

This letter is to advise that the Board of Management, at its Meeting held on 26 March 1992 considered the minutes of the Human Rights Committee Meeting held on 17 March 1992.

I am pleased to advise that the Board adopted the recommendation of the Human Rights Committee that the study proceed subject to the Statement of Informed Consent being amended to include the contact person's name, address and telephone number and said amendments being submitted to the Chairman of the Human Rights Committee.

I apologise for the delay in writing this letter and wish you well with this study.

Yours sincerely

G. Michael Galvin
A/DIRECTOR, CLINICAL SERVICES

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PC:VH

27 May 1992

Dr H.F. Oxer
Director
Hyperbaric Medicine Unit
Fremantle Hospital

Dear Dr Oxer

Re: "The Effect of Hyperbaric Oxygen on Carbon Monoxide Off-Gassing"

I apologise for not writing to you earlier following the Human Rights Committee's review of this protocol.

It was recommended to the Board that this protocol be accepted for implementation.

Yours sincerely

(Dr) Phillip Claringbold
CHAIRMAN, HUMAN RIGHTS COMMITTEE

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HUMAN RIGHTS COMMITTEE

PC/bb

10 June, 1992.

Dr. David Smart,
Senior Registrar,
Hyperbaric Medicine Unit,
Fremantle Hospital.

Dear Dr. Smart,

THE EFFECT OF HYPERBARIC OXYGEN ON CARBON MONOXIDE OFF-GASSING

Thank you for your letter of 29 May, 1992 together with copies of the amended Statements of Informed Consent which, I am pleased to advise, meet the requirements of the Human Rights Committee.

Sincerely yours,

Phillip Claringbold (Dr.),
Chairman,
HUMAN RIGHTS COMMITTEE

cc **Dr. H.F. Oxer**, Director, Hyperbaric Medicine Unit
Dr. P. Mark, Staff Specialist, Emergency Medicine

A62A

HEALTH WEST
CREATING A HEALTHIER STATE FOR EVERYBODY

FREMANTLE HOSPITAL and HEALTH SERVICE

VIVE VALEQUE

Executive Offices

HUMAN RESEARCH ETHICS COMMITTEE

wk

18 September 2002

Dr David Smart
GPO Box 463
Hobart
Tasmania 7001

Dear Dr Smart,

Re: The Effect of Hyperbaric Oxygen on Carbon Monoxide Offgassing.

I write further to your phone call to my office last week regarding the above study, which was approved by the former Research Committee and Human Rights Committee at Fremantle Hospital in 1992.

Attached is a copy of the Committee's terms of reference, a list of the Committee Membership and also a copy of the Committee's submission guidelines as requested.

I confirm that the Fremantle Hospital & Health Service Human Research Ethics Committee is constituted and functions in accordance with the NHMRC National Statement on Ethical Conduct in Research Involving Humans (1999).

If you need further information or clarification, please let me know.

Kind regards

Yours sincerely

Wendykho

WENDY KHOO
ADMINISTRATIVE OFFICER,
HUMAN RESEARCH ETHICS COMMITTEE

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APPENDIX 18.9 PRESENTATIONS AND PUBLICATIONS FROM THIS RESEARCH

(1) Abstract

Carbon Monoxide Offgassing. A new modality for assessing treatment endpoint.

Smart DR, Oxer HF, Mark PD, Banham NDG. *Emergency Medicine 1995;7:240*

(Paper awarded Micromedex prize for best free paper at the 12th Annual Scientific Meeting, Australasian College for Emergency Medicine, Fremantle, Western Australia, September 1995).

Copy of abstract from journal overleaf:

(2) Abstract

Carbon Monoxide Poisoning (Letter to editor). *Emergency Medicine* 2000; 12 : 354-357.

Copy of paper overleaf:

syndrome into three forms, a slowly progressive painless form with full thickness skin necrosis up to 50cm^2 or larger, an exquisitely painful form producing skin loss within 24 hours or pain and redness with no skin loss, and a form resulting in rapid skin discolouration, full thickness skin loss, gross swelling and systemic toxicity consisting of shock, prostration and severe diarrhoea.

This paper reviews all 13 published cases of suspected necrotising arachnidism in Australasia and a case of our own is reported. In five of these 14 cases, offending spiders were positively identified, three as *Lampona cylindrata* (white-tailed spider), one as *Badumna insignis* (window spider) and the other as genus *Steatoda* (the cupboard or brown house spider).

The abilities of various Australasian spider venoms to cause cutaneous necrosis and the management of necrotic arachnidism are discussed.

The implications of clinical practice guidelines

M Cleary

Department of Emergency Medicine, Royal Brisbane Hospital, Queensland

The United States of America's Institute of Medicine views clinical guidelines as systematically developed statements to assist practitioners make patient decisions about appropriate health care for specific clinical circumstances. This definition has been adopted by the National Health and Medical Research Council's (NHMRC) Quality of Care and Health Outcomes Committee as their Guidelines for the Development and Implementation of Clinical Practice Guidelines.

The issue that underpins the development of Clinical Practice Guidelines (CPGs) is the need to reduce the uncertainty about the optimal management for specified health problems. This uncertainty arises in two main areas, firstly the domain that relates to better health outcomes and secondly the need to ensure that health services are operated in a cost effective manner.

CPGs aim to promote appropriate management of specific health problems which should in turn lead to better health outcomes and a striking reduction in health care expenditure. They have principally been developed in the United States where they cover three broad areas of clinical practice:

- the doctor patient relationship and the area of medical negligence,
- the purchaser provider relationship and cost efficient standards of practice

and

- professional standards and the requirement to retain professional registration.

CPG development in Australia has been promoted by the Commonwealth and State departments of health through the NHMRC. To date this has been in close association with the professional bodies. This paper will describe Australian developments in this area.

Death, the coronial inquest and emergency medicine

S Young

Department of Emergency Medicine, Box Hill Hospital, Victoria

There are many people who die within hours of an attendance at an emergency department. Each state and territory of Australia has enacted specific legislation governing the reporting and investigation of such deaths. The legislation and the regulations concerning "reportable deaths", autopsies and inquests will be reviewed.

A coroner conducting an inquest into a "reportable death" must if possible determine the identity of the deceased, how death occurred, the cause of death and the identity of any person who contributed to the death. The coroner may then comment on any matter connected with the death including issues of public health or safety. Most coroners will disseminate information about contributing events or actions which, if remedied, may prevent death or serious injury to someone else in the future.

Because of the nature of emergency medicine, the coroner will investigate many people who have been managed by emergency physicians in the hours or days prior to their death. Valuable information concerning the accuracy and completeness of diagnosis, the adequacy of treatment and occurrence of complications may be revealed. There is an enormous potential for cooperation during this process.

A coroner often needs expert opinions concerning the emergency management of a deceased person. This may be merely an explanation of the diagnosis and procedures undergone or may involve an opinion regarding the adequacy of treatment. Commonly this advice is sought from a fellow of a medical college. Care must be exercised that the appropriate college is approached. Whilst it may be quite reasonable for an opinion to be sought from another college regarding emergency management in that specialty an opinion from an emergency physician should also be sought especially if criticism is forthcoming.

Whilst emergency physicians have considerable expertise in emergency medicine, few have much experience in presenting evidence in court. Training in the forensic aspects of emergency medicine is emerging and will be discussed.

A number of examples of Coronial Inquests into deaths of people who have died in or who have recently been seen in emergency departments will be presented. The outcomes in terms of recommendation and dissemination of information will be discussed.

Carbon monoxide off-gassing: a new modality for assessing the treatment endpoint in CO poisoning

DR Smart

Department of Emergency Medicine, Royal Hobart Hospital, Tasmania

HF Oxer, PD Mark, NDG Banham

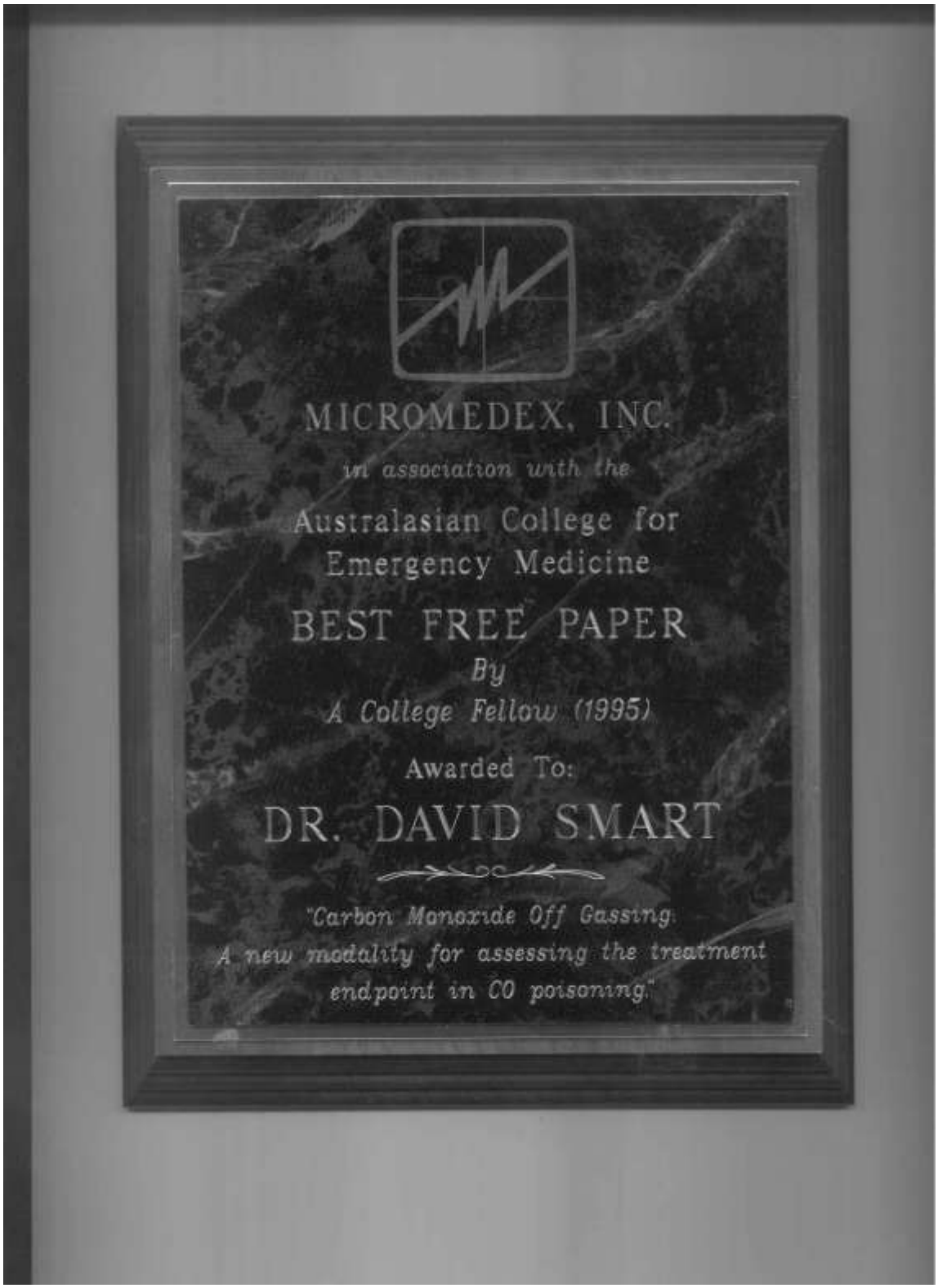
Department of Emergency Medicine, Fremantle Hospital, Western Australia

This prospective controlled study assessed CO off-gassing in patients' exhaled breath as a marker of CO poisoning, and its use as a treatment endpoint.

Patients were assigned to either 100% oxygen at one atmosphere (1ATA) or hyperbaric oxygen (HBO) at 2.8 ATA for 105 minutes. Patients receiving HBO treatment had more severe poisoning, that is COHb > 25%, loss of consciousness, clinical neurological abnormality or abnormality on mini mental state examination; otherwise they received 100% O_2 at 1ATA. Exhaled CO was continuously measured using a Drager data logger CO analyser (accuracy 1PPM). Treatment endpoints included zero off-gassing, or normalisation of the neuropsychological status, if this occurred later.

Sixty-four patients were eligible for the study from April 1992 to August 1993 at Fremantle Hospital. Five patients were referred for hyperbaric treatment more than 24 hours after CO exposure; all with severe neurological injury (GCS 3-9). Two of these patients died, three remained in a persistent vegetative state and one was lost to follow up. Fifty-eight patients treated within 12 hours of exposure had psychometric testing at two weeks and three months. Patients with abnormal screening tests were referred for more detailed testing by psychologists, blinded to the treatment. Fifteen patients in the series received 10% O_2 1ATA, and 43 received hyperbaric oxygen. An average of 8.5 hours of 100% O_2 1ATA was required to achieve zero off-gassing, versus a minimum of two treatments in the HBO treated group (range 2-5). Four out of 15 patients in the 100% O_2 1ATA group experienced delayed neuropsychological impairment compared with one out of 43 treated with HBO, ($p=0.013$, Fisher's exact test).

Zero CO off-gassing correlated well with normalisation of the acute neuropsychological status. It was not predictive of delayed impairment in either group, suggesting this syndrome is an indirect effect of CO. Hyperbaric oxygen treatment proved superior to 100% O_2 at 1ATA in preventing delayed relapses of cognitive function. All patients treated in less than 12 hours with hyperbaric oxygen had full recovery without relapse, when followed to three months.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BEST FREE PAPER
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DR. DAVID SMART
"Carbon Monoxide Off Gassing.
A new modality for assessing the treatment
endpoint in CO poisoning."

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(3) Abstract:

Hyperbaric Technicians and Nurses Association and Australian and New Zealand Hyperbaric Medicine Group 10th annual Scientific Meeting, Christchurch New Zealand August 2002

MEASUREMENT OF CARBON MONOXIDE (CO) ELIMINATION HALF LIFE USING EXPIRED CO (ECO) BREATH ANALYSIS, IN NBO AND HBO

David R Smart,
Royal Hobart Hospital, Hobart, Tasmania, Australia

Study Objectives

To measure elimination of CO in the breath of poisoned subjects and calculate elimination half-lives (T1/2) by measuring falling ECO concentrations, comparing NBO and 2.8 ATA HBO.

Methods

A Drager® datalogger CO analyser was used to measure ECO during treatment of poisoned patients. Five minutely measurement of RMV and ECO occurred, until subjects reached zero ECO. Elimination kinetics were calculated, and models tested for best fit included single phase and two phase exponential, and hyperbolic.

Results

Of 39 curves measured during HBO treatments, 38 had best fit with a single-phase exponential model. The same was true for 23 out of 24 elimination curves in NBO. The table shows the calculated T1/2 for each method. Mean HBO T1/2 were 37.2 minutes (95% CI 31.2-43.3), [ppm method] and 36.5 minutes (95% CI 30.0-42.9), [ml/minute method]. Mean NBO T1/2 were 144.6 minutes (95% CI 86.9-202.2) [ppm method] and 110.1 minutes (95% CI 70.8-149.4) [ml/minute method]. HBO T1/2 were significantly shorter than NBO T1/2; p=0.002. The range of HBO T1/2 varied 795%, and NBO T1/2 varied 616% between subjects. Smokers had a significant shorter CO elimination HBO T1/2, 33.5 minutes (25.8–41.2) compared to non-smokers 43.4 minutes (37.8-49.1), p=0.019.

Conclusions

Elimination of CO via the lungs is a single-phase exponential process, enhanced by increased P_IO_2. A highly significant difference in elimination T1/2 was noted for HBO vs NBO. The T1/2 calculated measuring ECO were of greater duration than those calculated for COHb by other authors. The large variation in CO elimination T1/2 has implications for treatment. This is the largest series measuring CO T1/2, and the first using ECO. Breath analysis is a practical method of measuring CO elimination.

(4) Abstract

Australasian College for Emergency Medicine, Winter Symposium, Melbourne, Australia July, 2003

UNDER PRESSURE: THE ROLE OF HYPERBARIC OXYGEN IN CARBON MONOXIDE POISONING

Dr David R Smart
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Calvary Health Care Tasmania
Medical Co-director of Diving and Hyperbaric Medicine
Royal Hobart Hospital Tasmania

Introduction
Definitive treatment of carbon monoxide poisoning has been controversial.

Objectives of Report
To review existing literature covering treatment of CO poisoning and provide treatment recommendations.

Methods
Literature from 1984 – 2003 was reviewed, examining mechanisms by which CO exerts its toxicity, and its elimination from the body. Clinical studies were analysed, including randomized controlled trials (RCT's), and the Cochrane review by Juurlink, to compare CO treatment outcomes [persistent neurological syndrome (PNS) and delayed neurological syndrome (DNS)], for hyperbaric oxygen and (HBO) and normobaric oxygen (NBO).

Results
HBO leads to faster removal of CO from the body, by reducing elimination half-life. RCT data from Weaver et al 2002 incorporated into the Cochrane review of Juurlink 2000, demonstrates a significant benefit in favour of HBO (OR for PNS after HBO is 0.68, 95%CI = 0.48 to 0.96). Number needed to treat = 13 to prevent one poor outcome. Subgroup analysis from Weaver favours HBO for LOC, COHb>25%, Age>50 yrs, or metabolic Acidosis. The only study favouring NBO (Scheinkestel et al) compared 72 atmosphere.hours treatment (NBO) to 80.5 atmosphere.hours treatment (HBO). Inpatient admission is required for three days a (ward only) cost of Au $796.00, compared to 24 hours if HBO is used. Two extra days inpatient care is greater than the marginal cost of three HBO treatments (Au $209.00 each). It is of concern that NBO treatment (based on Scheinkestel's study), has been implemented in some centres with sub-standard NBO regimens of < 24 hours.

Conclusions
HBO is a cost-effective treatment of CO poisoning, with outcomes supported by basic science and level 1 clinical evidence. Further research is needed to examine markers of treatment endpoint, and correlation of abnormal psychometric tests with functional status.

(5) Abstract and poster
Undersea and Hyperbaric Medicine Society Meeting Sydney, Australia May 25-30, 2004

USE OF EXPIRED CARBON MONOXIDE (ECO) TO DIAGNOSE ACUTE CO POISONING

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† FREMANTLE HOSPITAL, FREMANTLE, WESTERN AUSTRALIA

Aim

To investigate the use of ECO to diagnose acute CO poisoning in the Emergency Department, and to determine if poisoned individuals could be differentiated from non-poisoned smokers and non-smokers.

Methods

A system to measure ECO was developed using a Dräger Datalogger® with accuracy to 1 ppm [CO]. Measurement of ECO was preformed in real-time using controls (smokers and non-smokers) and poisoned individuals breathing air. ECO values were then evaluated to determine if poisoned and control groups could be differentiated.

Results

Twelve acutely (<6H) CO poisoned patients mean age 34.7 (95% CI = 28.8 to 40.5), 80 non-smoker controls mean age 26.6 (23.8 to 29.3) and 119 smoker controls mean age 32.8 (29.9 to 36.6) were enrolled in the study. Mean ECO values were: poisoned patients 66.17ppm (30.5 to 101.9), smokers 15.9ppm (14.1 to 17.8) and non-smokers 1.8ppm (1.5 to 2.1). ECO values were significantly different in each group ($p<0.0001$). In the diagnosis of acute CO poisoning, ECO>40ppm had a sensitivity of 0.67, specificity of 1.0, positive predictive value (PPV) of 1.0, and negative predictive value (NPV) of 0.98. For an ECO > 10ppm, sensitivity improved to 1.0, NPV = 1.0, at the expense of specificity = 0.63, and PPV = 0.14. The receiver operating characteristic curve for the ECO test had an area under the curve of 0.92.

Conclusions

ECO shows promise as a non-invasive method to diagnose acute CO poisoning, provided the ECO is > 40ppm. For values between 10 and 40ppm, clinical data is needed to interpret ECO results, to differentiate poisoned patients from smokers.

Use of expired carbon monoxide (ECO) to diagnose acute CO poisoning

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† Fremantle Hospital, Fremantle, Western Australia

Introduction

Carbon Monoxide poisoning has a non-specific clinical presentation. In up to one third of presentations, the diagnosis may be missed in the ED. Measurement of COHb requires an invasive procedure (blood sampling), which may not be appropriate if there is low index of suspicion of CO poisoning, and may be poorly tolerated by children. Carboxyhaemoglobin taken at the time of poisoning has proven unreliable as a marker of long-term outcome in CO poisoning. Severe CNS toxicity due to CO may be manifest, even when levels of COHb are low. Measurement of ECO is a non-invasive test and it is easily performed in the ED, sampling from a quietly breathing individual.

Figure 1 Apparatus for measuring expired CO (Inset: Dräger 190 Datalogger)

Aim

To investigate the use of ECO to diagnose acute CO poisoning in the Emergency Department, and to determine if poisoned individuals could be differentiated from non-poisoned smokers and non-smokers.

Method

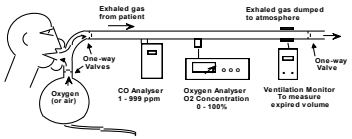
A system to measure ECO was developed using a Dräger Datalogger® with accuracy to 1 ppm [CO], in series with a Hudson Oxygen Analyser™ and a Bourns® LS75 ventilation Monitor to measure respiratory minute volume(Bourns Life Systems, California USA). The apparatus was configured to allow sampling from subjects breathing air, 100% oxygen (spontaneously breathing and ventilated), and HBO. Air samples only were collected in this section of the research.

Attached to a portable tray, the apparatus was able to obtain samples from individuals breathing air via the exhaled breath sampling port. Samples were obtained at one minute intervals over a five minute period, and the mean ECO recorded. Where poisoned individuals were already breathing 100% oxygen, a 5 to 10 minute air break was allowed, until the oxygen concentration in exhaled breath reached 21%. The ECO was then measured. The patient's clinical condition was carefully monitored during this period of reduced P_iO_2, to ensure that they did not deteriorate.

ECO samples were obtained from volunteer smokers, non-smokers and acutely poisoned individuals, and the values compared to determine sensitivity (Se), specificity (Sp), negative predictive value (NPV) and positive predictive values (PPV) for the test. A receiver operating characteristic (ROC) curve was also determined.

Approval was granted for the project by the Research and Ethics Committee of Fremantle Hospital (a teaching Hospital of the University of Western Australia).

Figure 2 Schematic diagram of apparatus



Results

Twelve acutely (<6H) CO poisoned patients mean age 34.7 (95% CI = 28.8 to 40.5), 80 non-smoker controls mean age 26.6 (23.8 to 29.3) and 119 smoker controls mean age 32.8 (29.9 to 36.6) were enrolled in the study.

Table 1 Demographics of the population studied

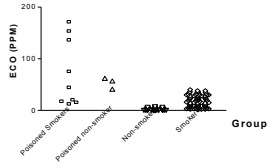
Control Population	Number	Mean Age (95% CI)	Age Range	Number of Females	Number of Males
(A) Non-smoker	80	32.8 (29.9-36.6)	13 to 74 years	44	36
(B) Smoker Controls	119	26.57 (23.8-29.3)	9 to 75 years	57	62
Acutely Poisoned Sample	12	34.7 (28.8-40.5)	19 to 59 years	3	9

ECO values were significantly different in each group ($p<0.0001$). In the diagnosis of acute CO poisoning, ECO > 40ppm had: Se = 0.67, Sp = 1.0, PPV = 1.0, and NPV= 0.98. For ECO > 10ppm, Se improved to 1.0, NPV = 1.0, at the expense of Sp = 0.63, and PPV = 0.14.

Table 2 Mean ECO and COHb values for the study population

Control Population	Mean COHb % (95% CI)	Mean ECO ppm (95% CI)
Non-smoker	0.06 (0.0 to 0.2)	1.8 (1.5 to 2.1)
Smoker Controls	2.8 (1.8 to 3.9)	15.94 (14.1- 17.8)
Acutely Poisoned Sample	16.3 (9.5 to 23.2)	66.2 (30.5-101.9)

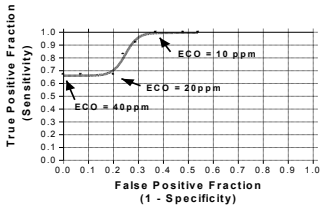
Figure 3 Graph showing spread of ECO values for each group



The receiver operating characteristic curve for the ECO test had an area under the curve of 0.92.

Figure 3

ROC curve for expired carbon monoxide used in the diagnosis of CO poisoning



Conclusion

ECO shows promise as a non-invasive method to diagnose acute CO poisoning, provided the ECO is > 40 ppm.

For values between 10 and 40ppm, clinical data is needed to interpret ECO results, to differentiate poisoned patients from smokers.

(6) Abstract
10th International Conference on Emergency Medicine, Cairns Australia, June 6-10, 2004

Monitoring of Exhaled Carbon Monoxide (ECO) is a useful method of determining treatment end-point in CO Poisoning.

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†Fremantle Hospital, Fremantle, Western Australia

Introduction
Treatment of CO poisoning is controversial. RCT's have applied a wide variation of oxygen doses. A reliable marker of treatment end-point for COP is yet to be identified. CO is excreted via the breath, and it is possible to measure this CO in real-time.

Aims
To investigate the prognostic value of titrating treatment of acute CO poisoning to an end-point of zero ECO, and to correlate patient status at treatment end-point with outcomes at three months.

Methods
Prospective cohort of consecutively enrolled acutely poisoned patients referred to a teaching hospital Emergency Department. Patients were allocated to receive HBO if LOC, COHb ≥25% (adults), ≥15% (children), Mini Mental State Examination (MMSE) ≤25, neurological abnormalities, cardiac arrhythmias. Using a Dräger Datalogger CO monitor, all patients received real-time measurement of ECO until it reached zero (treatment end-point). Clinical status was assessed post-treatment using GCS, MMSE, and psychometric testing. Assessment at 3 months with full psychometric evaluation was undertaken by clinical psychologists unaware of specific treatment. Outcomes were defined as normal, persistent early morbidity (PEM, mild, moderate and severe), delayed neurological syndrome (DNS), or death.

Results
Sixty six patients were eligible, four patients were excluded (3 refused entry, 1 non-acute). Two were lost to follow up. Sixty patients (93.4%) had full follow up, 47 were normal at treatment endpoint, of these, 46 (76.7%) had normal outcomes at 3 months. Four patients (6.6%) developed DNS, three recovered when retreated with HBO. Two patients (3.3%) died. Twelve had PEM at 3 months. Abnormal clinical status at treatment endpoint had a positive predictive value of 100% for poor outcome at 3 months. Clinical status at treatment endpoint predicted final outcome in 13/17 poor outcomes (sensitivity = 76%, specificity = 100%, negative predictive value = 94%). All false negative cases were DNS and three recovered when retreated with HBO. One DNS patient did not recover, and was also classified as PEM. Patients receiving HBO were more likely to develop DNS, than those receiving 100% oxygen [P=0.032, OR 0.078 (95%CI = 0.07 to 0.81)

Conclusions
Monitoring ECO until it is unrecordable constitutes a useful method of determining endpoint for treatment of CO poisoning. Three-month outcomes were consistent with other trials. Follow-up of patients with normal post-treatment status is required, because 8.5% in this series developed DNS.